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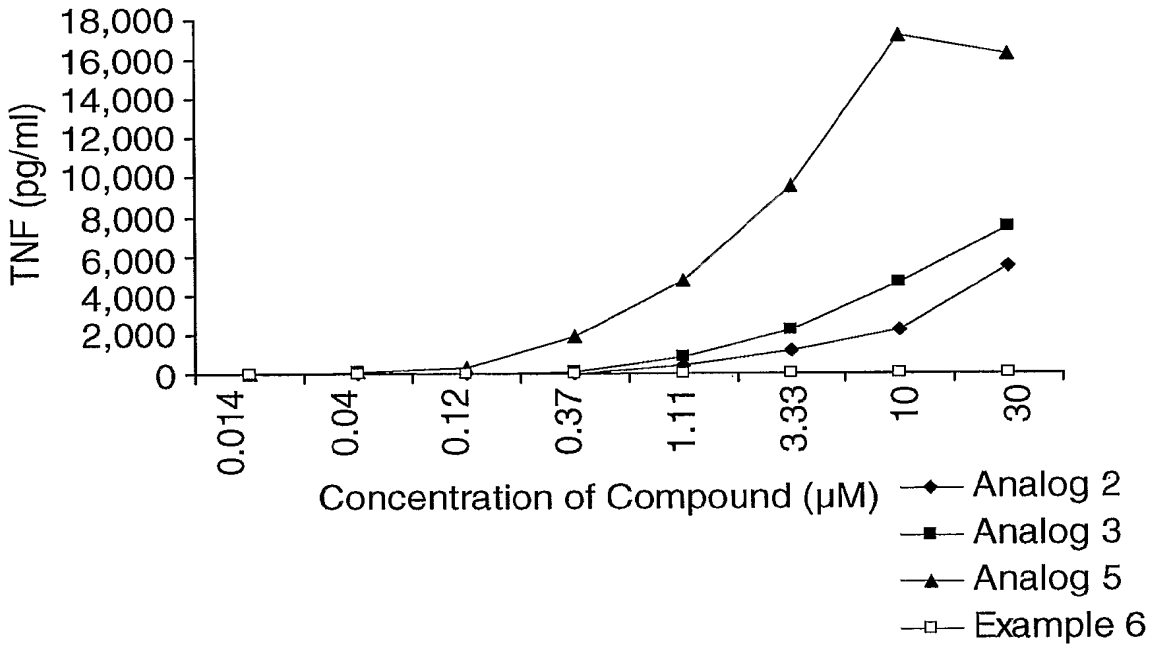
(54) Title: HYDROXYALKYL SUBSTITUTED IMIDAZOQUINOLINES



(57) Abstract: Certain imidazoquinolines with a hydroxymethyl or hydroxyethyl substituent at the 2-position, pharmaceutical compositions containing the compounds, intermediates, methods of making and methods of use of these compounds as immunomodulators, for preferentially inducing IFN-α biosynthesis in animals and in the treatment of diseases including viral and neoplastic diseases are disclosed.

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HYDROXYALKYL SUBSTITUTED IMIDAZOQUINOLINES

CROSS REFERENCE TO RELATED APPLICATIONS

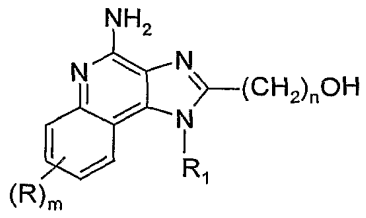
The present invention claims priority to U.S. Provisional Application Serial No. 60/655380, filed February 23, 2005, which is incorporated herein by reference.

BACKGROUND

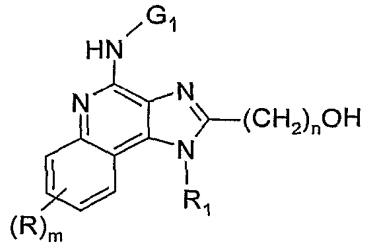
Certain compounds have been found to be useful as immune response modifiers (IRMs), rendering them useful in the treatment of a variety of disorders. However, there continues to be interest in and a need for compounds that have the ability to modulate the immune response, by induction of cytokine biosynthesis or other means.

SUMMARY

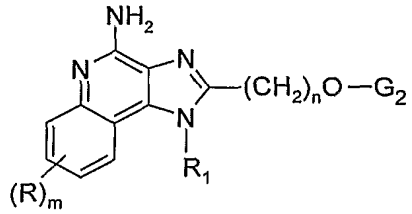
The present invention provides a new class of compounds which preferentially induce the biosynthesis of interferon (α) (IFN-α) in animals. Such compounds are of the following Formulas I, II, and III:



I



II



III

wherein R, R_1, G_1, G_2, m, and n are as defined below.

It has now surprisingly been discovered that the amount of TNF-α induced by the 2-(hydroxyalkyl) substituted compounds of the invention is substantially less than the amount of TNF-α induced by closely related analogs having an alkyl or alkyl ether substituent at the 2-position and that the compounds of the invention still retain the ability to induce the biosynthesis of IFN-α. See, for example, Figures 1-4 below. The reduction in the amount of TNF-α induced is seen over a broad range of test concentrations. In some embodiments the amount of TNF-α induced by the compounds of the invention is at least two-fold less than the amount of TNF-α induced by analogs having an alkyl or alkyl ether substituent at the 2-position. In other embodiments the amount of TNF-α induced by the compounds of the invention is at least three-fold less than the amount of TNF-α induced by analogs having an alkyl or alkyl ether substituent at the 2-position. In still other embodiments the amount of TNF-α induced by the compounds of the invention is at least four-fold less than the amount of TNF-α induced by analogs having an alkyl or alkyl ether substituent at the 2-position.

As used herein "substantially less than the amount of TNF-α " means that there is at least a two-fold reduction in the maximal TNF-α response as determined using the test methods described herein.

The compounds or salts of Formulas I, II, and III are especially useful as immune response modifiers due to their ability to preferentially induce interferon-α, thus providing a benefit over compounds that also induce pro-inflammatory cytokines (e.g. TNF-α) or that induce pro-inflammatory cytokines at higher levels.

A compound is said to preferentially induce IFN-α if, when tested according to the test methods described herein, the effective minimum concentration for IFN-α induction is less than the effective minimum concentration for TNF-α induction. In some embodiments, the effective minimum concentration for IFN-α induction is at least 3-fold less than the effective minimum concentration for TNF-α induction. In some

embodiments, the effective minimum concentration for IFN-α induction is at least 6-fold less than the effective minimum concentration for TNF-α induction. In other embodiments, the effective minimum concentration for IFN-α induction is at least 9-fold less than the effective minimum concentration for TNF-α induction. In some embodiments, when tested according to the test methods described herein, the amount TNF-α induced by compounds of the invention is at or below the background level of TNF-α in the test method.

The invention further provides pharmaceutical compositions containing an effective amount of a compound or salt of Formulas I, II, and/or III and methods of preferentially inducing the biosynthesis of IFN-α in an animal, and treating a viral infection or disease and/or treating a neoplastic disease in an animal by administering an effective amount of a compound or salt of Formulas I, II, and/or III or a pharmaceutical composition containing an effective amount of a compound or salt of Formulas I, II, and/or III to the animal.

In addition, methods of synthesizing compounds of Formulas I, II, and III and intermediates useful in the synthesis of these compounds are provided.

As used herein, "a," "an," "the," "at least one," and "one or more" are used interchangeably.

The terms "comprises" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. In several places throughout the description, guidance is provided through lists of examples, which examples can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the IFN-α dose response curves (corresponding to values shown in Table 5 below) for Example 6, Analog 2, Analog 3, and Analog 5.

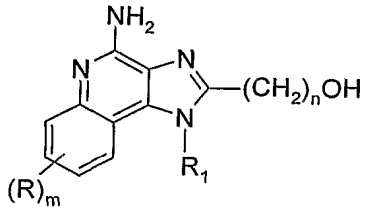
Figure 2 shows the TNF-α dose response curves (corresponding to values shown in Table 5 below) for Example 6, Analog 2, Analog 3, and Analog 5.

Figure 3 shows the IFN-α dose response curves (corresponding to values shown in Table 5 below) for Example 7, Analog 1, Analog 2, and Analog 4.

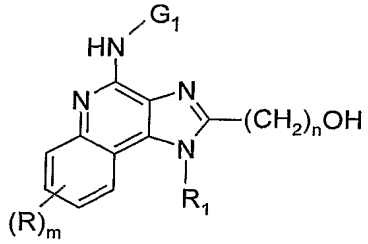
Figure 4 shows the TNF-α dose response curves (corresponding to values shown in Table 5 below) for Example 7, Analog 1, Analog 2, and Analog 4.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

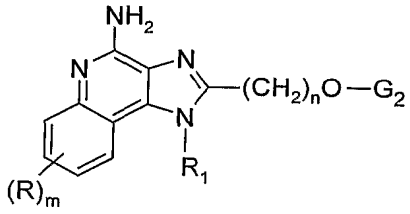
The present invention provides compounds of the following Formulas I, II, and III:



I



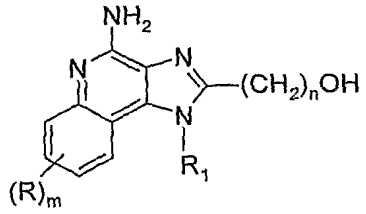
II



III

wherein R, R_1, G_1, G_2, m, and n are as defined below; and pharmaceutically acceptable salts thereof.

In one embodiment, the present invention provides a compound of the following Formula I:



I

wherein:

m is 0 or 1;

n is 1 or 2;

R is selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkoxy, halogen, and C_{1-10} haloalkyl;

R_1 is selected from the group consisting of:

-X-Y-R_4,

-X-R_5, and

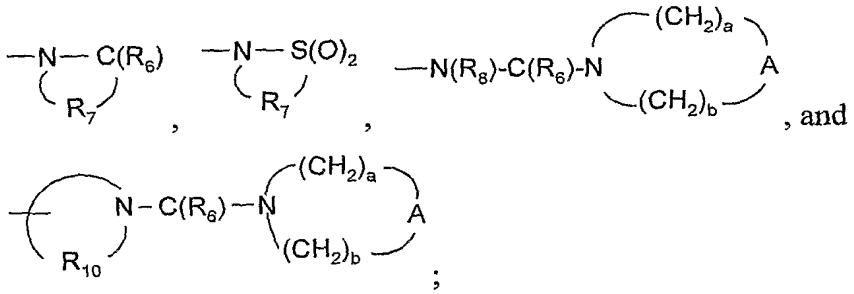
-X-Het;

X is straight chain or branched chain alkylene optionally interrupted by one -O- group;

Y is selected from the group consisting of -$S(O)_{0-2}$-and -$N(R_8)$-Q-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, and heteroarylalkylenyl, wherein the alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, and heteroarylalkylenyl, groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclyl, amino, alkylamino, dialkylamino, and in the case of alkyl and alkenyl, oxo;

R_5 is selected from the group consisting of:



;

Het is selected from the group consisting of tetrahydropyranyl and tetrahydrofuranyl;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_{10} is C_{3-8} alkylene;

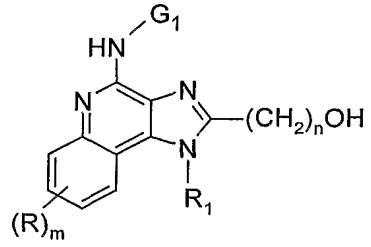
A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-S(O)_2$, $-C(R_6)-N(R_8)-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-S-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7;

with the proviso that when Y is $-S(O)_{0-2}-$ then X can not contain an -O- group; or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a compound of the following Formula II, which is a prodrug:



II

wherein:

G_1 is selected from the group consisting of:

-C(O)-R',

α-aminoacyl,

α-aminoacyl-α-aminoacyl,

-C(O)-O-R',

-C(O)-N(R")R',

-C(=NY')-R',

-CH(OH)-C(O)-OY',

$-CH(OC_{1-4}\text{ alkyl})Y_0$,

$-CH_2Y_1$, and

$-CH(CH_3)Y_1$;

R' and R" are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, phenyl, benzyl, and 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, aryl-C_{1-4} alkylenyl, heteroaryl-C_{1-4} alkylenyl, halo-C_{1-4} alkylenyl, halo-C_{1-4} alkoxy, $-O-C(O)-CH_3$, $-C(O)-O-CH_3$, $-C(O)-NH_2$, $-O-CH_2-C(O)-NH_2$, $-NH_2$, and $-S(O)_2-NH_2$, with the proviso that R" can also be hydrogen;

α-aminoacyl is an α-aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids;

Y' is selected from the group consisting of hydrogen, C_{1-6} alkyl, and benzyl;

Y_0 is selected from the group consisting of C_{1-6} alkyl, carboxy-C_{1-6} alkylenyl, amino-C_{1-4} alkylenyl, mono-*N*-C_{1-6} alkylamino-C_{1-4} alkylenyl, and di-*N,N*-C_{1-6} alkylamino-C_{1-4} alkylenyl;

Y_1 is selected from the group consisting of mono-*N*-C_{1-6} alkylamino, di-*N,N*-C_{1-6} alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C_{1-4} alkylpiperazin-1-yl;

m is 0 or 1;

n is 1 or 2;

R is selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkoxy, halogen, and C_{1-10} haloalkyl;

R_1 is selected from the group consisting of:

$-X-Y-R_4$,

$-X-R_5$, and

-X-Het;

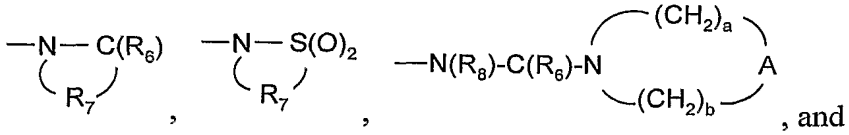
X is straight chain or branched chain alkylene optionally interrupted by one -O- group;

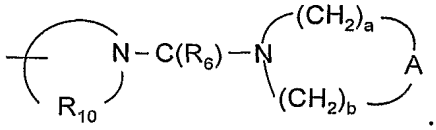
Y is selected from the group consisting of $-S(O)_{0-2}-$and $-N(R_8)-Q-$;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, and heteroarylalkylenyl, wherein the alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, and heteroarylalkylenyl, groups can be unsubstituted or

substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclyl, amino, alkylamino, dialkylamino, and in the case of alkyl and alkenyl, oxo;

R_5 is selected from the group consisting of:


, and


;

Het is selected from the group consisting of tetrahydropyranyl and tetrahydrofuranyl;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_{10} is C_{3-8} alkylene;

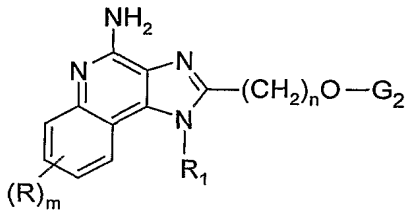
A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-S-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

with the proviso that when Y is $-S(O)_{0-2}-$ then X can not contain an -O- group; or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a compound of the following Formula III, which is a prodrug:



III

wherein:

G_2 is selected from the group consisting of:

$-X_2-C(O)-R'$,

α-aminoacyl,

α-aminoacyl-α-aminoacyl,

$-X_2-C(O)-O-R'$, and

$-C(O)-N(R'')R'$;

X_2 is selected from the group consisting of a bond; $-CH_2-O-$; $-CH(CH_3)-O-$; $-C(CH_3)_2-O-$; and, in the case of $-X_2-C(O)-O-R'$, $-CH_2-NH-$;

R' and R'' are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, phenyl, benzyl, and 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, aryl-C_{1-4} alkylenyl, heteroaryl-C_{1-4} alkylenyl, halo-C_{1-4} alkylenyl, halo-C_{1-4} alkoxy, $-O-C(O)-CH_3$, $-C(O)-O-CH_3$, $-C(O)-NH_2$, $-O-CH_2-C(O)-NH_2$, $-NH_2$, and $-S(O)_2-NH_2$, with the proviso that R'' can also be hydrogen;

α-aminoacyl is an α-aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids;

m is 0 or 1;

n is 1 or 2;

R is selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkoxy, halogen, and C_{1-10} haloalkyl;

R_1 is selected from the group consisting of:

$-X-Y-R_4$,

$-X-R_5$, and

-X-Het;

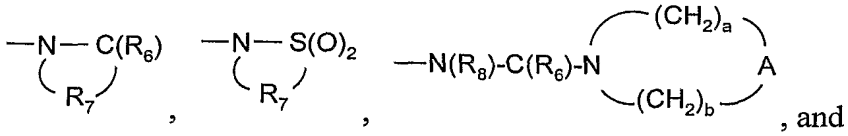
X is straight chain or branched chain alkylene optionally interrupted by one -O- group;

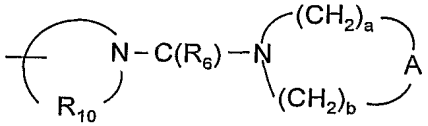
Y is selected from the group consisting of $-S(O)_{0-2}-$and $-N(R_8)-Q-$;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, and heteroarylalkylenyl, wherein the alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, and heteroarylalkylenyl, groups can be unsubstituted or

substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclyl, amino, alkylamino, dialkylamino, and in the case of alkyl and alkenyl, oxo;

R_5 is selected from the group consisting of:


, and


;

Het is selected from the group consisting of tetrahydropyranyl and tetrahydrofuranyl;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-S(O)_2$, $-C(R_6)-N(R_8)-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-S-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b \leq 7$;

with the proviso that when Y is $-S(O)_{0-2}-$ then X can not contain an -O- group; or a pharmaceutically acceptable salt thereof.

Unless otherwise specified, as used herein, the terms "alkyl", "alkenyl", "alkynyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, e.g., cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms, and alkynyl groups containing from 2 to 20 carbon atoms. In some embodiments, these groups have a total of up to 10 carbon atoms, up to 8 carbon atoms, up to 6 carbon

atoms, or up to 4 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclobutyl, cyclopropylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cyclohexylmethyl, adamantyl, and substituted and unsubstituted bornyl, norbornyl, and norbornenyl.

Unless otherwise specified, "alkylene", "alkenylene", and "alkynylene" are the divalent forms of the "alkyl", "alkenyl", and "alkynyl" groups defined above. The terms, "alkylenyl", "alkenylenyl", and "alkynylenyl" are use when "alkylene", "alkenylene", and "alkynylene," respectively, are substituted. For example, an arylalkylenyl group comprises an alkylene moiety to which an aryl group is attached.

The term "haloalkyl" is inclusive of groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of other groups that include the prefix "halo-." Examples of suitable haloalkyl groups are chloromethyl, chlorobutyl, trifluoromethyl, 2,2,2-trifluoroethyl, and the like.

The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl.

Unless otherwise indicated, the term "heteroatom" refers to the atoms O, S, or N.

The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N). In some embodiments, the term "heteroaryl" includes a ring or ring system that contains 2-12 carbon atoms, 1-3 rings, 1-4 heteroatoms, and O, S, and N as the heteroatoms. Exemplary heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxalinyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, pyrazinyl, 1-oxidopyridyl, pyridazinyl, triazinyl, tetrazinyl, oxadiazolyl, thiadiazolyl, and so on.

The term "heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. In some embodiments, the term "heterocyclyl" includes a ring or ring system that contains 2-12 carbon atoms, 1-3 rings, 1-4 heteroatoms, and O, S, and N as the heteroatoms. Exemplary heterocyclyl groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, 1,1-

dioxothiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, tetrahydropyranyl, quinuclidinyl, homopiperidinyl (azepanyl), 1,4-oxazepanyl, homopiperazinyl (diazepanyl), 1,3-dioxolanyl, aziridinyl, azetidinyl, dihydroisoquinolin-(1*H*)-yl, octahydroisoquinolin-(1*H*)-yl, dihydroquinolin-(2*H*)-yl, octahydroquinolin-(2*H*)-yl, dihydro-1*H*-imidazolyl, 3-azabicyclo[3.2.2]non-3-yl, and the like.

The term "heterocyclyl" includes bicylic and tricyclic heterocyclic ring systems. Such ring systems include fused and/or bridged rings and spiro rings. Fused rings can include, in addition to a saturated or partially saturated ring, an aromatic ring, for example, a benzene ring. Spiro rings include two rings joined by one spiro atom and three rings joined by two spiro atoms.

When "heterocyclyl" contains a nitrogen atom, the point of attachment of the heterocyclyl group may be the nitrogen atom.

The terms "arylene", "heteroarylene", and "heterocyclylene" are the divalent forms of the "aryl", "heteroaryl", and "heterocyclyl" groups defined above. The terms, "arylenyl", "heteroarylenyl", and "heterocyclylenyl" are used when "arylene", "heteroarylene", and "heterocyclylene", respectively, are substituted. For example, an alkylarylenyl group comprises an arylene moiety to which an alkyl group is attached.

When a group (or substituent or variable) is present more than once in any Formula described herein, each group (or substituent or variable) is independently selected, whether explicitly stated or not. For example, for the formula -N(R_8)-C(O)-N(R_8)- each R_8 group is independently selected.

The invention is inclusive of the compounds described herein in any of their pharmaceutically acceptable forms, including isomers (e.g., diastereomers and enantiomers), salts, solvates, polymorphs, and the like. In particular, if a compound is optically active, the invention specifically includes each of the compound's enantiomers as well as racemic mixtures of the enantiomers. It should be understood that the term "compound" includes any or all of such forms, whether explicitly stated or not (although at times, "salts" are explicitly stated).

The term "prodrug" means a compound that can be transformed in vivo to yield an immune response modifying compound, including any of the salt, solvated, polymorphic, or isomeric forms described above. The prodrug, itself, may be an immune response

modifying compound, including any of the salt, solvated, polymorphic, or isomeric forms described above. The transformation may occur by various mechanisms, such as through a chemical (e.g., solvolysis or hydrolysis, for example, in the blood) or enzymatic biotransformation. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A. C. S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For any of the compounds presented herein, each one of the following variables (e.g., Y, X, R_1, Q, G_1, G_2, n, and so on) in any of its embodiments can be combined with any one or more of the other variables in any of their embodiments and associated with any one of the formulas described herein, as would be understood by one of skill in the art. Each of the resulting combinations of variables is an embodiment of the present invention.

For certain embodiments of Formula I, II, or III, n is 1.

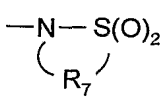
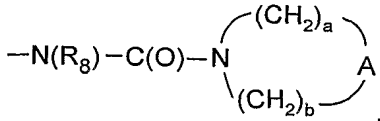
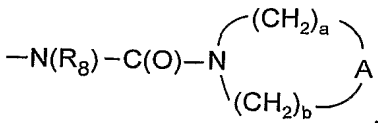
For certain embodiments of Formula I, II, or III, n is 2.

For certain embodiments of Formula I, II, or III, including any one of the above embodiments, m is 0.

For certain embodiments of Formula I, II, or III, including any one of the above embodiments, R_1 is -X-Y-R_4 wherein X is straight chain or branched chain C_{1-6} alkylene which may be interrupted by one -O- group; Y is selected from the group consisting of -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, -N(R_8)-C(O)-N(R_8)-, and -S(O)$_2$- wherein R_8 is selected from hydrogen and methyl; and R_4 is selected from the group consisting of C_{1-6} alkyl, isoquinolinyl, *N*-methylimidazolyl, pyridinyl, quinolinyl, phenyl, and phenyl substituted by a substituent selected from the group consisting of chloro, cyano, fluoro, hydroxy, and methyl; with the proviso that when Y is -S(O)$_2$- then X can not contain an -O- group. For certain of these embodiments, as well as any one of the above embodiments, R_1 is selected from the group consisting of 2-[(cyclopropylcarbonyl)amino]ethyl, 4-[(cyclopropylcarbonyl)amino]butyl, 2-[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-{[(1-methylethyl)carbonyl]amino}ethyl, 4-{[(1-methylethyl)carbonyl]amino}butyl, 2-methyl-2-{[(1-methylethyl)carbonyl]amino}propyl, 2-[(methylsulfonyl)amino]ethyl, 4-[(methylsulfonyl)amino]butyl, 2-methyl-2-[(methylsulfonyl)amino]propyl, 2-methyl-2-

({[(1-methylethyl)amino]carbonyl}amino)propyl, and 2,2-dimethyl-3-(methylsulfonyl)propyl.

For certain embodiment, including any one of the above embodiments of Formulas I, II, and III, R_1 is -X-Y-R_4 wherein X is straight chain or branched chain C_{1-8} alkylene which may be interrupted by one -O- group; Y is selected from the group consisting of -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, -N(R_8)-S(O)$_2$-N(R_{8a})-, -N(R_8)-C(O)-N(R_{8a})-, and -S(O)$_2$- wherein R_8 is hydrogen, methyl, benzyl, or pyridin-3-ylmethyl; R_{8a} is hydrogen, methyl, or ethyl, and R_4 is selected from the group consisting of C_{1-7} alkyl, haloC_{1-4} alkyl, hydroxyC_{1-4} alkyl, phenyl, benzyl, 1-phenylethyl, 2-phenylethyl, 2-phenylethenyl, phenylcyclopropyl, pyridinyl, thienyl, *N*-methylimidazolyl, 3,5-dimethylisoxazolyl, wherein benzyl is unsubstituted or substituted by a methyl group, and phenyl is unsubstituted or substituted by one or two substituents independently selected from the group consisting of methyl, fluoro, chloro, cyano, hydroxy, and dimethylamino; with the proviso that when Y is -S(O)$_2$- then X can not contain an -O- group. For certain of these embodiments, Y is selected from the group consisting of -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, and -N(R_8)-C(O)-N(R_{8a})-. For certain of these embodiments, R_{8a} is hydrogen. Alternatively, for certain of these embodiments, R_{8a} is methyl. For certain of these embodiments, R_8 is hydrogen. Alternatively, for certain of these embodiments, R_8 is benzyl. Alternatively, for certain of these embodiments, R_8 is pyridin-3-ylmethyl. Alternatively, for certain of these embodiments, Y is -S(O)$_2$-. For certain of these embodiments, X is C_{1-6} alkylene.

For certain embodiments of Formula I, II, or III, including any one of the above embodiments except where R_1 is -X-Y-R_4, R_1 is -X-R_5, wherein X is straight chain or branched chain C_{1-6} alkylene, and R_5 is  or  . For certain of these embodiments, R_5 is  . For certain of these embodiments, R_8 is hydrogen, methyl, or pyridin-3-ylmethyl, A is -O-, -CH_2-, or -N(CH_3)-, a is 1 or 2, and b is 2. For certain of these embodiments, R_1 is selected from the group consisting of 4-(1,1-dioxidoisothiazolidin-2-yl)butyl, 4-[(4-morpholinecarbonyl)amino]butyl, and 2-[(4-morpholinecarbonyl)amino]ethyl.

For certain embodiments of Formula I, II, or III, including any one of the above embodiments except where R_1 is -X-Y-R_4 or -X-R_5, R_1 is -C_{1-4} alkylenyl-Het. For certain of these embodiments, as well as any one of the above embodiments where Het is present, Het is selected from the group consisting of tetrahydropyranyl and tetrahydrofuranyl. For certain of these embodiments, as well as any one of the above embodiments where Het is present, R_1 is tetrahydro-2*H*-pyran-4-ylmethyl.

For certain embodiments, for example, embodiments of Formula I, the present invention provides a compound selected from the group consisting of *N*-[4-(4-amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]methanesulfonamide and *N*-{4-[4-amino-2-(2-hydroxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl]}methanesulfonamide, or a pharmaceutically acceptable salt thereof.

For certain embodiments, for example, embodiments of Formula I, the present invention provides *N*-{2-[4-amino-2-(hydroxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1,1-dimethylethyl}methanesulfonamide or a pharmaceutically acceptable salt thereof.

For certain embodiments, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of Formula I, II, III, or of any one of the above embodiments and a pharmaceutically acceptable carrier.

For certain embodiments, the present invention provides a method of preferentially inducing the biosynthesis of IFN-α in an animal comprising administering an effective amount of a compound or salt of Formula I, II, III, or of any one of the above embodiments or the above pharmaceutical composition to the animal.

For certain embodiments, the present invention provides a method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of Formula I, II, III, or of any one of the above embodiments or the above pharmaceutical composition to the animal.

For certain embodiments, the present invention provides a method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of Formula I, II, III, or of any one of the above embodiments or the above pharmaceutical composition to the animal.

For certain embodiments of the above methods, the compound or salt or pharmaceutical composition is administered systemically.

For certain embodiments, R is selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkoxy, halogen, and C_{1-10} haloalkyl.

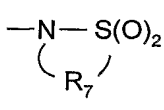
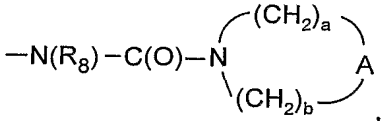
For certain embodiments, R_1 is selected from the group consisting of -X-Y-R_4, -X-R_5, and -X-Het.

For certain embodiments, R_1 is -X-Y-R_4.

For certain embodiments, R_1 is -X-Y-R_4 wherein X is straight chain or branched chain C_{1-6} alkylene which may be interrupted by one -O- group; Y is selected from the group consisting of -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, -N(R_8)-C(O)-N(R_8)-, and -S(O)$_2$- wherein R_8 is selected from hydrogen and methyl; and R_4 is selected from the group consisting of C_{1-6} alkyl, isoquinolinyl, *N*-methylimidazolyl, pyridinyl, quinolinyl, phenyl, and phenyl substituted by a substituent selected from the group consisting of chloro, cyano, fluoro, hydroxy, and methyl.

For certain embodiments, R_1 is selected from the group consisting of 2-[(cyclopropylcarbonyl)amino]ethyl, 4-[(cyclopropylcarbonyl)amino]butyl, 2-[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-{[(1-methylethyl)carbonyl]amino}ethyl, 4-{[(1-methylethyl)carbonyl]amino}butyl, 2-methyl-2-{[(1-methylethyl)carbonyl]amino}propyl, 2-[(methylsulfonyl)amino]ethyl, 4-[(methylsulfonyl)amino]butyl, 2-methyl-2-[(methylsulfonyl)amino]propyl, 2-methyl-2-({[(1-methylethyl)amino]carbonyl}amino)propyl, and 2,2-dimethyl-3-(methylsulfonyl)propyl.

For certain embodiments, R_1 is -X-R_5.

For certain embodiments, R_1 is -X-R_5 wherein X is straight chain or branched chain C_{1-6} alkylene, and R_5 is  or  .

For certain embodiments, R_1 is selected from the group consisting of 4-(1,1-dioxidoisothiazolidin-2-yl)butyl, 4-[(4-morpholinecarbonyl)amino]butyl, and 2-[(4-morpholinecarbonyl)amino]ethyl.

For certain embodiments, R_1 is -X-Het.

For certain embodiments, R_1 is -C_{1-4} alkylenyl-Het.

For certain embodiments, R_1 is tetrahydro-2*H*-pyran-4-ylmethyl.

For certain embodiments, R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, and heteroarylalkylenyl, wherein the alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, and heteroarylalkylenyl, groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclyl, amino, alkylamino, dialkylamino, and in the case of alkyl and alkenyl, oxo.

For certain embodiments, R_4 is selected from the group consisting of C_{1-6} alkyl, isoquinolinyl, *N*-methylimidazolyl, pyridinyl, quinolinyl, phenyl, and phenyl substituted by a substituent selected from the group consisting of chloro, cyano, fluoro, hydroxy, and methyl.

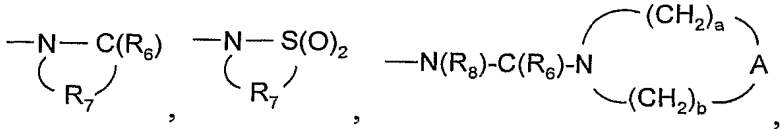
For certain embodiments, R_4 is selected from the group consisting of C_{1-7} alkyl, haloC_{1-4} alkyl, hydroxyC_{1-4} alkyl, phenyl, benzyl, 1-phenylethyl, 2-phenylethyl, 2-phenylethenyl, phenylcyclopropyl, pyridinyl, thienyl, *N*-methylimidazolyl, 3,5-dimethylisoxazolyl, wherein benzyl is unsubstituted or substituted by a methyl group, and phenyl is unsubstituted or substituted by one or two substituents independently selected from the group consisting of methyl, fluoro, chloro, cyano, hydroxy, and dimethylamino.

For certain embodiments, R_4 is C_{1-7} alkyl.

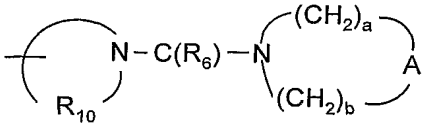
For certain embodiments, R_4 is C_{1-4} alkyl.

For certain embodiments, R_4 is phenyl which is unsubstituted or substituted by one or two substituents independently selected from the group consisting of methyl, fluoro, chloro, cyano, hydroxy, and dimethylamino.

For certain embodiments, R_5 is selected from the group consisting of



, and



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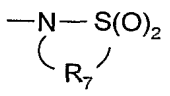
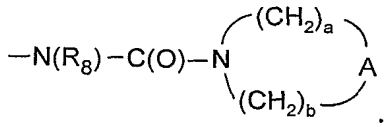
For certain embodiments, R_5 is 

or 

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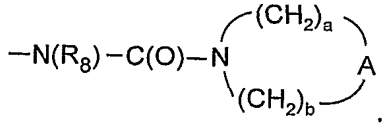
For certain embodiments, R_5 is  .

For certain embodiments, R_6 is selected from the group consisting of =O and =S.

For certain embodiments, R_6 is =O.

For certain embodiments, R_6 is =S.

For certain embodiments, R_7 is C_{2-7} alkylene.

For certain embodiments, R_7 is C_{2-4} alkylene.

For certain embodiments, R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl.

For certain embodiments, R_8 is selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} alkoxyC_{1-4} alkylenyl.

For certain embodiments, R_8 is arylalkylenyl.

For certain embodiments, R_8 is benzyl.

For certain embodiments, R_8 is heteroarylalkylenyl.

For certain embodiments, R_8 is pyridin-3-ylmethyl.

For certain embodiments, R_8 is hydrogen or C_{1-4} alkyl.

For certain embodiments, R_8 is selected from hydrogen and methyl

For certain embodiments, R_8 is hydrogen.

For certain embodiments, R_{10} is C_{3-8} alkylene.

For certain embodiments, R_{10} is C_{4-6} alkylene.

For certain embodiments, A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$.

For certain embodiments, A is -O-, $-CH_2-$, or $-N(Q-R_4)-$.

For certain embodiments, A is -O-, $-CH_2-$, -S-, or $-S(O)_2-$.

For certain embodiments, A is -O- or $-S(O)_2-$.

For certain embodiments, A is -O-.

For certain embodiments, A is $-CH_2-$.

For certain embodiments, A is $-N(Q-R_4)-$.

For certain embodiments, A is $-N(CH_3)-$.

For certain embodiments, including any one of the above embodiments of Formula II, G_1 is selected from the group consisting of -C(O)-R', α-aminoacyl, α-aminoacyl-α-aminoacyl, -C(O)-O-R', -C(O)-N(R")R', -C(=NY')-R', -CH(OH)-C(O)-OY', -CH(OC_{1-4} alkyl)Y_0, -CH_2Y_1, and -$CH(CH_3)Y_1$; R' and R" are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, phenyl, benzyl, and 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, aryl-C_{1-4} alkylenyl, heteroaryl-C_{1-4} alkylenyl, halo-C_{1-4} alkylenyl, halo-C_{1-4} alkoxy, -O-C(O)-CH_3, -C(O)-O-CH_3, -C(O)-NH_2, -O-CH_2-C(O)-NH_2, -NH_2, and –$S(O)_2$-NH_2, with the proviso that R" can also be hydrogen; α-aminoacyl is an α-aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids; Y' is selected from the group consisting of hydrogen, C_{1-6} alkyl, and benzyl; Y_0 is selected from the group consisting of C_{1-6} alkyl, carboxy-C_{1-6} alkylenyl, amino-C_{1-4} alkylenyl, mono-*N*-C_{1-6} alkylamino-C_{1-4} alkylenyl, and di-*N,N*-C_{1-6} alkylamino-C_{1-4} alkylenyl; and Y_1 is selected from the group consisting of mono-*N*-C_{1-6} alkylamino, di-*N,N*-C_{1-6} alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C_{1-4} alkylpiperazin-1-yl.

For certain embodiments, including any one of the above embodiments of Formula II, G_1 is selected from the group consisting of -C(O)-R', α-aminoacyl, and -C(O)-O-R'. For certain of these embodiments, R' contains one to ten carbon atoms. For certain of these embodiments, α-aminoacyl is an α-C_{2-11} aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids containing a total of at least 2 carbon atoms and a total of up to 11 carbon atoms, and may also include one or more heteroatoms selected from the group consisting of O, S, and N.

For certain embodiments, including any one of the above embodiments of Formula III, G_2 is selected from the group consisting of -X_2-C(O)-R', α-aminoacyl, α-aminoacyl-α-aminoacyl, -X_2-C(O)-O-R', and -C(O)-N(R")R'. For certain of these embodiments, X_2 is selected from the group consisting of a bond; -CH_2-O-; -$CH(CH_3)$-O-; -$C(CH_3)_2$-O-; and, in the case of -X_2-C(O)-O-R', -CH_2-NH-; R' and R" are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, phenyl, benzyl, and 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently

selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, aryl-C_{1-4} alkylenyl, heteroaryl-C_{1-4} alkylenyl, halo-C_{1-4} alkylenyl, halo-C_{1-4} alkoxy, -O-C(O)-CH_3, -C(O)-O-CH_3, -C(O)-NH_2, -O-CH_2-C(O)-NH_2, -NH_2, and –$S(O)_2$-NH_2, with the proviso that R" can also be hydrogen; and α-aminoacyl is an α-aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids.

For certain embodiments, including any one of the above embodiments of Formula III, G_2 is selected from the group consisting of -C(O)-R' and α-aminoacyl, wherein R' is C_{1-6} alkyl or phenyl which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, aryl-C_{1-4} alkylenyl, heteroaryl-C_{1-4} alkylenyl, halo-C_{1-4} alkylenyl, halo-C_{1-4} alkoxy, -O-C(O)-CH_3, -C(O)-O-CH_3, -C(O)-NH_2, -O-CH_2-C(O)-NH_2, -NH_2, and –$S(O)_2$-NH_2.

For certain embodiments, including any one of the above embodiments of Formula III, G_2 is selected from the group consisting of α-amino-C_{2-5} alkanoyl, C_{2-6} alkanoyl, C_{1-6} alkoxycarbonyl, and C_{1-6} alkylcarbamoyl.

For certain embodiments, including any one of the above embodiments which include an α-aminoacyl group, α-aminoacyl is an α-aminoacyl group derived from a naturally occuring α-amino acid selected from the group consisting of racemic, D-, and L-amino acids.

For certain embodiments, including any one of the above embodiments which include an α-aminoacyl group, α-aminoacyl is an α-aminoacyl group derived from an α-amino acid found in proteins, wherein the the amino acid is selected from the group consisting of racemic, D-, and L-amino acids.

For certain embodiments, the hydrogen atom of the hydroxy group of Formula II (including any one of its embodiments) is replaced by G_2, wherein G_2 is defined as in any one of the above embodiments of G_2.

For certain embodiments, Het is selected from the group consisting of tetrahydropyranyl and tetrahydrofuranyl.

For certain embodiments, Het is tetrahydro-2*H*-pyran-4-yl.

For certain embodiments, Q is selected from the group consisting of a bond, -$C(R_6)$-, -$S(O)_2$, -$C(R_6)$-$N(R_8)$-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, and -$C(R_6)$-S-.

For certain embodiments, Q is selected from the group consisting of a bond, $-C(R_6)-$, $-S(O)_2-$, and $-C(R_6)-N(R_8)-$.

For certain embodiments, Q is selected from the group consisting of $-C(O)-$, $-S(O)_2-$, and $-C(O)-N(R_8)-$. In certain of these embodiments, R_8 is hydrogen or methyl.

For certain embodiments, Q is $-C(O)-$.

For certain embodiments, Q is $-S(O)_2-$.

For certain embodiments, Q is $-C(R_6)-N(R_8)-$.

For certain embodiments, Q is $-C(O)-N(R_8)-$ wherein R_8 is hydrogen or methyl.

For certain embodiments, X is straight chain or branched chain alkylene optionally interrupted by one -O- group.

For certain embodiments, X is straight chain or branched chain C_{1-6} alkylene which may be interrupted by one -O- group.

For certain embodiments, X is straight chain or branched chain C_{1-8} alkylene.

For certain embodiments, X is straight chain or branched chain C_{1-6} alkylene.

For certain embodiments, X is straight chain or branched chain C_{1-4} alkylene.

For certain embodiments, X is ethylene.

For certain embodiments, X is propylene.

For certain embodiments, X is butylene.

For certain embodiments, X is $-CH_2-C(CH_3)_2-$.

For certain embodiments, Y is selected from the group consisting of $-S(O)_{0-2}-$and $-N(R_8)-Q-$, with the proviso that when Y is $-S(O)_{0-2}-$ then X does not contain an -O- group.

For certain embodiments, Y is selected from the group consisting of $-N(R_8)-C(O)-$, $-N(R_8)-S(O)_2-$, $-N(R_8)-C(O)-N(R_8)-$, and $-S(O)_2-$, with the proviso that when Y is $-S(O)_2-$ then X does not contain an -O- group. In certain of these embodiments, R_8 is selected from hydrogen and methyl.

For certain embodiments, Y is selected from the group consisting of $-N(R_8)-C(O)-$, $-N(R_8)-S(O)_2-$, $-N(R_8)-S(O)_2-N(R_{8a})-$, $-N(R_8)-C(O)-N(R_{8a})-$, and $-S(O)_2-$.

For certain embodiments, Y is selected from the group consisting of $-N(R_8)-C(O)-$, $-N(R_8)-S(O)_2-$, $-N(R_8)-C(O)-N(R_{8a})-$.

For certain embodiments, Y is $-S(O)_2-$.

For certain embodiments, a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7.

For certain embodiments, a and b are each independently 1 to 3.

For certain embodiments, a and b are each 2.

For certain embodiments, a is 1, 2, or 3, and b is 2.

For certain embodiments, a is 1 or 2, and b is 2.

For n certain embodiments, n is 1 or 2.

For certain embodiments, n is 1.

For certain embodiments, n is 2.

For certain embodiments, m is 0 or 1.

For certain embodiments, m is 0.

For certain embodiments, m is 1.

Preparation of the Compounds

Compounds of the invention may be synthesized by synthetic routes that include processes analogous to those well known in the chemical arts, particularly in light of the description contained herein. The starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, Wisconsin, USA) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, *Reagents for Organic Synthesis*, v. 1-19, Wiley, New York, (1967-1999 ed.); Alan R. Katritsky, Otto Meth-Cohn, Charles W. Rees, *Comprehensive Organic Functional Group Transformations*, v. 1-6, Pergamon Press, Oxford, England, (1995); Barry M. Trost and Ian Fleming, *Comprehensive Organic Synthesis*, v. 1-8, Pergamon Press, Oxford, England, (1991); or *Beilsteins Handbuch der organischen Chemie*, 4, Aufl. Ed. Springer-Verlag, Berlin, Germany, including supplements (also available via the Beilstein online database)).

For illustrative purposes, the reaction schemes depicted below provide potential routes for synthesizing the compounds of the present invention as well as key intermediates. For more detailed description of the individual reaction steps, see the EXAMPLES section below. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the compounds of the invention. Although specific starting materials and reagents are depicted in the reaction schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by

the methods described below can be further modified in light of this disclosure using conventional methods well known to those skilled in the art.

In the preparation of compounds of the invention it may sometimes be necessary to protect a particular functionality while reacting other functional groups on an intermediate. The need for such protection will vary depending on the nature of the particular functional group and the conditions of the reaction step. Suitable amino protecting groups include acetyl, trifluoroacetyl, *tert*-butoxycarbonyl (Boc), benzyloxycarbonyl, and 9-fluorenylmethoxycarbonyl (Fmoc). Suitable hydroxy protecting groups include acetyl and silyl groups such as the *tert*-butyl dimethylsilyl group. For a general description of protecting groups and their use, see T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, USA, 1991.

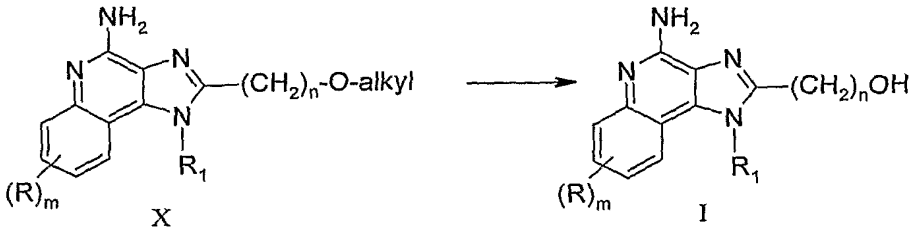
Conventional methods and techniques of separation and purification can be used to isolate compounds of the invention, as well as various intermediates related thereto. Such techniques may include, for example, all types of chromatography (high performance liquid chromatography (HPLC), column chromatography using common absorbents such as silica gel, and thin layer chromatography), recrystallization, and differential (i.e., liquid-liquid) extraction techniques.

In some embodiments, compounds of the invention can be prepared according to Reaction Scheme I, wherein R_1, R, m, and n are as defined above and alkyl is methyl or ethyl.

In Reaction Scheme I an ether substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula X is cleaved to provide a hydroxyalkyl substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula I. The reaction is conveniently carried out by adding a solution of boron tribromide in a suitable solvent such as dichloromethane to a solution or suspension of a compound of Formula X in a suitable solvent such as dichloromethane at ambient or at a sub-ambient temperature, for example, at 0°C. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Numerous compounds of Formula X are known; others can be prepared using known synthetic methods. See, for example, United States Patent Nos. 6,069,149; 6,331,539; 6,451,810; 6,541,485; 6,756,382; 6,677,349; 6,573,273; 6,664,264; 6,664,265; 6,677,347; 6,660,735; 6,683,088; and 6,667,312 and the references cited therein.

Reaction Scheme I

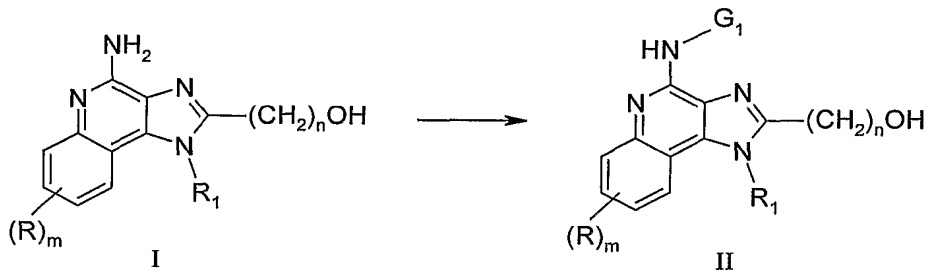


In some embodiments, compounds of the invention can be prepared according to Reaction Scheme II, wherein R_1, G_1, and n are as defined above. Compounds of Formula I can be prepared according to the method described above. The amino group of a compound of Formula I can be converted by conventional methods to a functional group such as an amide, carbamate, urea, amidine, or another hydrolyzable group. A compound of this type can be made by the replacement of a hydrogen atom in an amino group with a group such as -C(O)-R', α-aminoacyl, α-aminoacyl-α-aminoacyl, -C(O)-O-R', -C(O)-N(R")R', -C(=NY')-R', -CH(OH)-C(O)-OY', -CH(OC_{1-4} alkyl)Y_0, -CH_2Y_1, and -CH(CH_3)Y_1; wherein R' and R" are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, phenyl, benzyl, and 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, aryl-C_{1-4} alkylenyl, heteroaryl-C_{1-4} alkylenyl, halo-C_{1-4} alkylenyl, halo-C_{1-4} alkoxy, -O-C(O)-CH_3, -C(O)-O-CH_3, -C(O)-NH_2, -O-CH_2-C(O)-NH_2, -NH_2, and –$S(O)_2$-NH_2, with the proviso that R" can also be hydrogen; each α-aminoacyl is an α-aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids; Y' is selected from the group consisting of hydrogen, C_{1-6} alkyl, and benzyl; Y_0 is selected from the group consisting of C_{1-6} alkyl, carboxy-C_{1-6} alkylenyl, amino-C_{1-4} alkylenyl, mono-*N*-C_{1-6} alkylamino-C_{1-4} alkylenyl, and di-*N,N*-C_{1-6} alkylamino-C_{1-4} alkylenyl; and Y_1 is selected from the group consisting of mono-*N*-C_{1-6} alkylamino, di-*N,N*-C_{1-6} alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C_{1-4} alkylpiperazin-1-yl. Particularly useful compounds of Formula II are amides derived from carboxylic acids containing one to ten carbon atoms, amides derived from amino acids, and carbamates containing one to ten carbon atoms. The reaction can be carried out, for example, by combining a compound of Formula I with a

chloroformate or acid chloride, such as ethyl chloroformate or acetyl chloride, in the presence of a base such as triethylamine in a suitable solvent such as dichloromethane at ambient temperature.

Alternatively, the hydroxy group on a compound of Formula I can be protected using a suitable silyl group such as *tert*-butyl dimethylsilyl using conventional methods. The G_1 group may then be installed using conventional methods followed by the removal of the hydroxy protecting group under acidic conditions to provide a compound of Formula II.

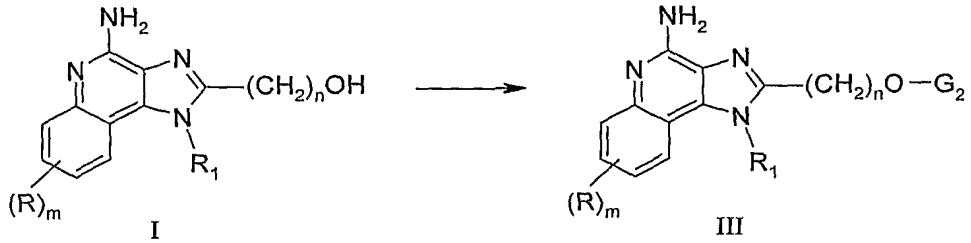
Reaction Scheme II



In some embodiments, compounds of the invention can be prepared according to Reaction Scheme III, wherein R_1, G_2, and n are as defined above. Compounds of Formula I can be prepared according to the method described above. The hydrogen atom of the alcohol group of a compound of Formula I can be replaced using conventional methods with a group such as X_2-C(O)-R', α-aminoacyl, α-aminoacyl-α-aminoacyl, -X_2-C(O)-O-R', and -C(O)-N(R")R'; wherein X_2 is selected from the group consisting of a bond; -CH_2-O-; -$CH(CH_3)$-O-; -$C(CH_3)_2$-O-; and, in the case of -X_2-C(O)-O-R', -CH_2-NH-; R' and R" are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, phenyl, benzyl, and 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, aryl-C_{1-4} alkylenyl, heteroaryl-C_{1-4} alkylenyl, halo-C_{1-4} alkylenyl, halo-C_{1-4} alkoxy, -O-C(O)-CH_3, -C(O)-O-CH_3, -C(O)-NH_2, -O-CH_2-C(O)-NH_2, -NH_2, and –$S(O)_2$-NH_2, with the proviso that R" can also be hydrogen; and each α-aminoacyl is an α-aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids. Particularly useful compounds of Formula III are esters made from carboxylic acids

containing one to six carbon atoms, unsubstituted or substituted benzoic acid esters, or esters made from naturally occurring amino acids. For example, the reaction can be carried out by treating a compound of Formula I with a carboxylic acid or amino acid under Mitsunobu reaction conditions by adding triphenylphosphine and a carboxylic acid to a solution or suspension of a compound of Formula I in a suitable solvent such as tetrahydrofuran and then slowly adding diisopropyl azodicarboxylate. The reaction can be run at a sub-ambient temperature such as 0 °C.

Reaction Scheme III



I III

In some embodiments, compounds of the invention can also be prepared using the synthetic methods described in the EXAMPLES below.

Pharmaceutical Compositions and Biological Activity

Pharmaceutical compositions of the invention contain a therapeutically effective amount of a compound or salt described above in combination with a pharmaceutically acceptable carrier.

The terms "a therapeutically effective amount" and "effective amount" mean an amount of the compound or salt sufficient to induce a therapeutic or prophylactic effect, such as cytokine induction, immunomodulation, antitumor activity, and/or antiviral activity. Cytokine induction can include preferentially inducing the biosynthesis of IFN-α. The exact amount of compound or salt used in a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art, such as the physical and chemical nature of the compound or salt, the nature of the carrier, and the intended dosing regimen.

In some embodiments, the compositions of the invention will contain sufficient active ingredient or prodrug to provide a dose of about 100 nanograms per kilogram (ng/kg) to about 50 milligrams per kilogram (mg/kg), preferably about 10 micrograms per kilogram (μg/kg) to about 5 mg/kg, of the compound or salt to the subject.

In other embodiments, the compositions of the invention will contain sufficient active ingredient or prodrug to provide a dose of, for example, from about 0.01 mg/m^2 to about 5.0 mg/m^2, computed according to the Dubois method, in which the body surface area of a subject (m^2) is computed using the subject's body weight: $m^2 = (wt\ kg^{0.425} \times height\ cm^{0.725}) \times 0.007184$, although in some embodiments the methods may be performed by administering a compound or salt or composition in a dose outside this range. In some of these embodiments, the method includes administering sufficient compound to provide a dose of from about 0.1 mg/m^2 to about 2.0 mg/m^2 to the subject, for example, a dose of from about 0.4 mg/m^2 to about 1.2 mg/m^2.

A variety of dosage forms may be used, such as tablets, lozenges, capsules, parenteral formulations (e.g., intravenous formulations), syrups, creams, ointments, aerosol formulations, transdermal patches, transmucosal patches and the like. These dosage forms can be prepared with conventional pharmaceutically acceptable carriers and additives using conventional methods, which generally include the step of bringing the active ingredient into association with the carrier.

The compounds or salts of the invention can be administered as the single therapeutic agent in the treatment regimen, or the compounds or salts described herein may be administered in combination with one another or with other active agents, including additional immune response modifiers, antivirals, antibiotics, antibodies, proteins, peptides, oligonucleotides, etc.

Compounds or salts of the invention have been shown to induce the production of certain cytokines in experiments performed according to the tests set forth below. These results indicate that the compounds or salts are useful for modulating the immune response in a number of different ways, rendering them useful in the treatment of a variety of disorders. The compounds or salts of the invention are especially useful as immune response modifiers due to their ability to preferentially induce interferon-α, thus providing a benefit over compounds that also induce pro-inflammatory cytokines (e.g. TNF-α) or that induce pro-inflammatory cytokines at higher levels. While interferon-α and pro-inflammatory cytokines are beneficial in treating certain conditions, interferon-α preferentially induced is believed to be better tolerated by patients, because the significantly lower levels of pro-inflammatory cytokines can result in fewer or less severe adverse side effects experienced by patients. For example, if a subject is treated for a

disease (e.g., hepatitis C, metastatic cancer) with a compound that induces significant levels of pro-inflammatory cytokines, while treating the disease, the compound may also cause side effects, such as severe and/or widespread inflammation, tissue destruction, or emesis, that render the subject unable or unwilling to receive the treatment. Alternatively, if a subject is treated with a compound that preferentially induces interferon-α then the compound may treat the disease with less risk of adverse side effects from pro-inflammatory cytokines such as TNF-α. Therefore, by maintaining the ability to treat a condition and reducing adverse side effects, compounds that preferentially induce IFN-α provide an advantage over compounds that would also induce pro-inflammatory cytokines, such as TNF-α, at higher levels.

The ability of the compounds or salts of the invention to preferentially induce the biosynthesis of IFN-α may be particularly advantageous when administered systemically, since adverse side effects, including for example widespread inflammation, may be reduced or even eliminated. Compounds of the invention may be administered systemically in a number of ways, including but not limited to oral and intravenous administration.

Cytokines whose biosynthesis may be induced by compounds or salts of the invention include IFN-α, IP-10, MCP-1, and a variety of other cytokines. In some instances, cytokines such as TNF-α, IL-12 may be induced, albeit at significantly reduced levels. Among other effects, these and other cytokines can inhibit virus production and tumor cell growth, making the compounds or salts useful in the treatment of viral diseases and neoplastic diseases. Accordingly, the invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of the invention to the animal. The animal to which the compound or salt is administered for induction of cytokine biosynthesis may have a disease as described *infra*, for example a viral disease or a neoplastic disease, and administration of the compound or salt may provide therapeutic treatment. Alternatively, the compound or salt may be administered to the animal prior to the animal acquiring the disease so that administration of the compound or salt may provide a prophylactic treatment.

In addition to the ability to induce the production of cytokines, compounds or salts of the invention can affect other aspects of the innate immune response. For example, the

compounds or salts may cause maturation of dendritic cells or proliferation and differentiation of B-lymphocytes.

Whether for prophylaxis or therapeutic treatment of a disease, and whether for effecting innate or acquired immunity, the compound or salt or composition may be administered alone or in combination with one or more active components as in, for example, a vaccine adjuvant. When administered with other components, the compound or salt or composition and other component or components may be administered separately; together but independently such as in a solution; or together and associated with one another such as (a) covalently linked or (b) non-covalently associated, e.g., in a colloidal suspension.

Conditions for which compounds or salts or compositions identified herein may be used as treatments include, but are not limited to:

(a) viral diseases such as, for example, diseases resulting from infection by an adenovirus, a herpesvirus (e.g., HSV-I, HSV-II, CMV, or VZV), a poxvirus (e.g., an orthopoxvirus such as variola or vaccinia, or molluscum contagiosum), a picornavirus (e.g., rhinovirus or enterovirus), an orthomyxovirus (e.g., influenzavirus), a paramyxovirus (e.g., parainfluenzavirus, mumps virus, measles virus, and respiratory syncytial virus (RSV)), a coronavirus (e.g., SARS), a papovavirus (e.g., papillomaviruses, such as those that cause genital warts, common warts, or plantar warts), a hepadnavirus (e.g., hepatitis B virus), a flavivirus (e.g., hepatitis C virus or Dengue virus), or a retrovirus (e.g., a lentivirus such as HIV);

(b) bacterial diseases such as, for example, diseases resulting from infection by bacteria of, for example, the genus Escherichia, Enterobacter, Salmonella, Staphylococcus, Shigella, Listeria, Aerobacter, Helicobacter, Klebsiella, Proteus, Pseudomonas, Streptococcus, Chlamydia, Mycoplasma, Pneumococcus, Neisseria, Clostridium, Bacillus, Corynebacterium, Mycobacterium, Campylobacter, Vibrio, Serratia, Providencia, Chromobacterium, Brucella, Yersinia, Haemophilus, or Bordetella;

(c) other infectious diseases, such as chlamydia, fungal diseases including but not limited to candidiasis, aspergillosis, histoplasmosis, cryptococcal meningitis, or parasitic diseases including but not limited to malaria, pneumocystis carnii pneumonia, leishmaniasis, cryptosporidiosis, toxoplasmosis, and trypanosome infection;

(d) neoplastic diseases, such as intraepithelial neoplasias, cervical dysplasia, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, renal cell carcinoma, Kaposi's sarcoma, melanoma, leukemias including but not limited to acute myeloid leukemia, acute lymphocytic leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, B-cell lymphoma, and hairy cell leukemia, and other cancers;

(e) T_H2-mediated, atopic diseases, such as atopic dermatitis or eczema, eosinophilia, asthma, allergy, allergic rhinitis, and Ommen's syndrome;

(f) certain autoimmune diseases such as systemic lupus erythematosus, essential thrombocythaemia, multiple sclerosis, discoid lupus, alopecia areata; and

(g) diseases associated with wound repair such as, for example, inhibition of keloid formation and other types of scarring (e.g., enhancing wound healing, including chronic wounds).

Additionally, a compound or salt identified herein may be useful as a vaccine adjuvant for use in conjunction with any material that raises either humoral and/or cell mediated immune response, such as, for example, live viral, bacterial, or parasitic immunogens; inactivated viral, tumor-derived, protozoal, organism-derived, fungal, or bacterial immunogens; toxoids; toxins; self-antigens; polysaccharides; proteins; glycoproteins; peptides; cellular vaccines; DNA vaccines; autologous vaccines; recombinant proteins; and the like, for use in connection with, for example, BCG, cholera, plague, typhoid, hepatitis A, hepatitis B, hepatitis C, influenza A, influenza B, parainfluenza, polio, rabies, measles, mumps, rubella, yellow fever, tetanus, diphtheria, hemophilus influenza b, tuberculosis, meningococcal and pneumococcal vaccines, adenovirus, HIV, chicken pox, cytomegalovirus, dengue, feline leukemia, fowl plague, HSV-1 and HSV-2, hog cholera, Japanese encephalitis, respiratory syncytial virus, rotavirus, papilloma virus, yellow fever, and Alzheimer's Disease.

Compounds or salts identified herein may be particularly helpful in individuals having compromised immune function. For example, compounds or salts may be used for treating the opportunistic infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

Thus, one or more of the above diseases or types of diseases, for example, a viral disease or a neoplastic disease may be treated in an animal in need thereof (having the

disease) by administering a therapeutically effective amount of a compound or salt of the invention to the animal.

An animal may also be vaccinated by administering an effective amount of a compound or salt described herein, as a vaccine adjuvant. In one embodiment, there is provided a method of vaccinating an animal comprising administering an effective amount of a compound or salt described herein to the animal as a vaccine adjuvant.

An amount of a compound or salt effective to induce cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as dendritic cells and B-cells to produce an amount of one or more cytokines such as, for example, IFN-α, IP-10, and MCP-1 that is increased (induced) over a background level of such cytokines. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. In other embodiments, the amount is expected to be a dose of, for example, from about 0.01 mg/m^2 to about 5.0 mg/m^2, (computed according to the Dubois method as described above) although in some embodiments the induction of cytokine biosynthesis may be performed by administering a compound or salt in a dose outside this range. In some of these embodiments, the method includes administering sufficient compound or salt or composition to provide a dose of from about 0.1 mg/m^2 to about 2.0 mg/m^2 to the subject, for example, a dose of from about 0.4 mg/m^2 to about 1.2 mg/m^2.

The invention provides a method of treating a disease which is responsive to the induction of cytokine biosynthesis, particularly the preferential induction of IFN-α, including a method of treating a viral infection in an animal and a method of treating a neoplastic disease in an animal, comprising administering an effective amount of a compound or salt or composition of the invention to the animal. An amount effective to treat or inhibit a viral infection is an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount that is effective for such treatment will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. An amount of a compound or salt effective to treat a neoplastic condition is an amount that will cause a reduction in tumor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected

to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. In other embodiments, the amount is expected to be a dose of, for example, from about 0.01 mg/m^2 to about 5.0 mg/m^2, (computed according to the Dubois method as described above) although in some embodiments either of these methods may be performed by administering a compound or salt in a dose outside this range. In some of these embodiments, the method includes administering sufficient compound or salt to provide a dose of from about 0.1 mg/m^2 to about 2.0 mg/m^2 to the subject, for example, a dose of from about 0.4 mg/m^2 to about 1.2 mg/m^2.

In addition to the formulations and uses described specifically herein, other formulations, uses, and administration devices suitable for compounds of the present invention are described in, for example, International Publication Nos. WO 03/077944 and WO 02/036592, U.S. Patent No. 6,245,776, and U.S. Publication Nos. 2003/0139364, 2003/185835, 2004/0258698, 2004/0265351, 2004/076633, and 2005/0009858.

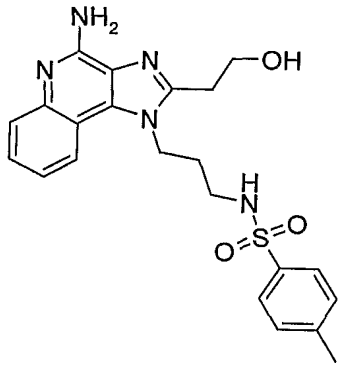
Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

EXAMPLES

In the examples below normal high performance flash chromatography (prep HPLC) was carried out using a COMBIFLASH system (an automated high-performance flash purification product available from Teledyne Isco, Inc., Lincoln, Nebraska, USA) or a HORIZON HPFC system (an automated high-performance flash purification product available from Biotage, Inc, Charlottesville, Virginia, USA). The eluent used for each purification is given in the example. In some chromatographic separations, the solvent mixture 80/18/2 v/v/v chloroform/methanol/concentrated ammonium hydroxide (CMA) was used as the polar component of the eluent. In these separations, CMA was mixed with chloroform in the indicated ratio.

Example 1

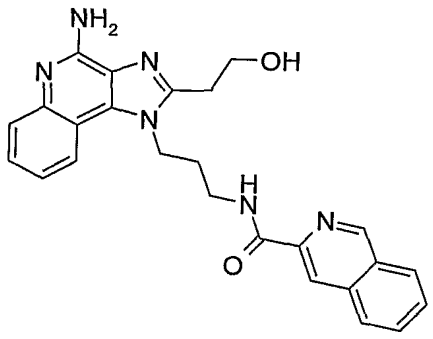
N-{3-[4-Amino-2-(2-hydroxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}-4-methylbenzenesulfonamide



Boron tribromide (5.50 mL of 1 M in dichloromethane) was added dropwise to a chilled (0 °C) suspension of *N*-{3-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}-4-methylbenzenesulfonamide (1.0 g, 2.2 mmol; U.S. Patent No. 6,677,349, Example 253) in dichloromethane (20 mL). The reaction mixture was stirred at 0 °C for 3 hours. The reaction mixture was quenched with methanol. Hydrochloric acid (about 10 mL of 6 N) was added and the mixture was stirred at 50 °C overnight. The mixture was diluted with water (50 mL) and ethyl acetate (100 mL) and then brought to neutral pH with solid sodium hydroxide. The layers were separated and the aqueous was extracted with ethyl acetate (x2). The combined organics were dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide a yellow solid. This material was purified by prep HPLC (COMBIFLASH system eluting first with a gradient of 0 to 5% methanol in dichloromethane containing 1% ammonium hydroxide and then with a gradient of 5 to 10% methanol in dichloromethane containing 1% ammonium hydroxide) to provide a white solid. This material was suspended in hot acetonitrile, allowed to cool, and then the solvent was decanted. The resulting material was dried under vacuum to provide about 200 mg of *N*-{3-[4-amino-2-(2-hydroxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}-4-methylbenzenesulfonamide as a white solid, m.p.231-232 °C. Anal. calcd for $C_{22}H_{25}N_5O_3S \cdot 0.20\ CH_4O$: %C, 59.79; %H, 5.85; %N, 15.70. Found: %C, 59.44; %H, 5.89; %N, 15.52.

Example 2

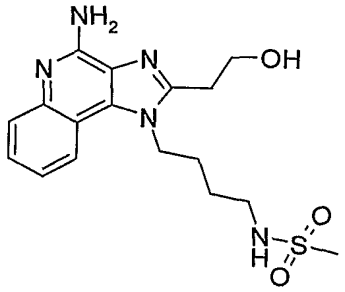
N-{3-[4-Amino-2-(2-hydroxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}isoquinoline-3-carboxamide



Boron tribromide (5.50 mL of 1 M in dichloromethane) was added dropwise to a chilled (0 °C) suspension of *N*-{3-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}isoquinoline-3-carboxamide (1.0 g, 2.2 mmol; U.S. Patent No. 6,756,382, Example 192) in dichloromethane (20 mL). The reaction mixture was stirred at 0 °C for 45 minutes and then allowed to warm to ambient temperature. After 5 hours the reaction mixture was concentrated under reduced pressure and the residue was allowed to stand over the weekend. The residue was diluted with methanol (20 mL) and then heated to 50 °C. Hydrochloric acid (about 10 mL of 6 N) was added and the mixture was stirred for about 2.5 hours. The mixture was made basic with aqueous sodium hydroxide and then extracted with ethyl acetate (x2). The combined extracts were dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide a yellow solid. This material was purified by prep HPLC (COMBIFLASH system eluting first with a gradient of 0 to 5% methanol in dichloromethane containing 1% ammonium hydroxide and then with a gradient of 5 to 10% methanol in dichloromethane containing 1% ammonium hydroxide) to provide a white solid. This material was suspended in hot acetonitrile, allowed to cool, and then the solvent was decanted. The resulting material was dried under vacuum to provide about 400 mg of *N*-{3-[4-amino-2-(2-hydroxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}isoquinoline-3-carboxamide as a white solid, mp 245-246 °C. Anal calcd for $C_{25}H_{24}N_6O_2$: %C, 67.73; %H, 5.59; %N, 18.80; Found: %C, 67.38; %H, 5.54; %N, 18.84.

Example 3

N-{4-[4-Amino-2-(2-hydroxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}methanesulfonamide



Part A

3-Methoxypropionyl chloride (15.4 g, 126 mmol) was added dropwise over a period of 20 minutes to a chilled (ice bath) solution of *tert*-butyl *N*-{4-[(3-aminoquinolin-4-yl)amino]butyl}carbamate (38 g, 115 mmol, U.S. Patent No. 6,541,485, Example 2, Part B) in pyridine. The reaction mixture was stirred for 4 hours and then allowed to stand at ambient temperature over the weekend. Pyridine hydrochloride (3.9 g, 34 mmol) was added and the reaction mixture was heated at reflux overnight. The reaction mixture was concentrated under reduced pressure and the residue was diluted with dichloromethane (250 mL) and aqueous sodium bicarbonate (250 mL). The layers were separated. The separatory funnel was rinsed with a small amount of methanol to remove a residue coating the walls. The combined organics were concentrated under reduced pressure. The residue was purified by prep HPLC (COMBIFLASH system eluting first with a gradient of 0 to 5% methanol in dichloromethane containing 1% ammonium hydroxide and then with a gradient of 5 to 10% methanol in dichloromethane containing 1% ammonium hydroxide) to provide 18 g of *tert*-butyl *N*-{4-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}carbamate.

Part B

3-Chloroperoxybenzoic acid (20 g of 77%) was added in a single portion to a solution of the material from Part A (18 g, 45.2 mmol) in dichloroethane (170 mL). After 2 hours concentrated ammonium hydroxide (150 mL) was added and the reaction mixture was stirred until the phases were mixed well. *Para*-Toluenesulfonyl chloride (10.6 g, 54 mmol) was added in a single portion along with a small amount of dichloroethane. The reaction mixture was stirred overnight at ambient temperature and then diluted with water

and dichloromethane. The layers were separated and the aqueous layer was extracted with dichloromethane (x2). The combined organics were dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide 23 g of crude *tert*-butyl *N*-{4-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}carbamate as a red tar.

Part C

The material from Part B was combined with a solution of hydrochloric acid in dioxane (325 mL of 4 M) and stirred at ambient temperature for 3 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in methanol (30 mL) and 6 M sodium hydroxide was added with stirring to about pH 9. Attempts to extract with dichloromethane and ethyl acetate were not successful. The organic and aqueous layers were concentrated under reduced pressure and combined to provide a dark orange solid. This material was purified by prep HPLC (COMBIFLASH system eluting first with a gradient of 0 to 8% methanol in dichloromethane containing 1% ammonium hydroxide and then with a gradient of 9 to 35% methanol in dichloromethane containing 1% ammonium hydroxide) to provide 10.65 g of 1-(4-aminobutyl)-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as an orange solid.

Part D

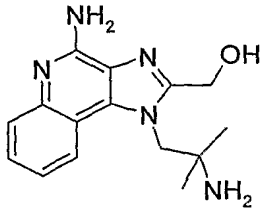
Triethylamine (10.5 mL, 75.0 mmol) was added to a mixture of a portion (4.7 g, 15 mmol) of the material from Part C in pyridine (50 mL). The reaction mixture was stirred for several minutes and then methanesulfonyl chloride (1.27 mL, 16.5 mmol) was added dropwise. The reaction mixture was stirred at ambient temperature for 2 hours and then at 50 °C for 2 hours. More methanesulfonyl chloride (0.5 eq) was added and the reaction mixture was stirred at 50 °C for 2 hours. Another portion of methanesulfonyl chloride (0.25 eq) was added and the reaction mixture was stirred at ambient temperature overnight. The reaction mixture was diluted with dichloromethane and water. The layers were separated and the aqueous layer was extracted with dichloromethane (x3). The combined organics were dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide 5 g of crude *N*-{4-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}methanesulfonamide as a red oil.

Part E

Boron tribromide (22.4 mL of 1 M in dichloromethane) was added slowly to a chilled (ice bath) mixture of a portion of the material from Part D (3.5 g, about 8.9 mmol) and dichloromethane (50 mL). After the addition was complete the ice bath was removed and the reaction mixture was allowed to stir at ambient temperature for 3 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in methanol and then combined with hydrochloric acid (50 mL of 6 M). The mixture was stirred at 50 °C for 2 hours and then concentrated under reduced pressure. The residue was combined with ammonia in methanol (about 50 mL of 7 M) to neutralize the acid and then concentrated. This procedure was repeated 3 times. The crude product was purified by prep HPLC (COMBIFLASH system eluting with a gradient of 0 to 10% methanol in dichloromethane containing 1% ammonium hydroxide). The product was stirred with hot acetonitrile, allowed to stand overnight, and then isolated by filtration, washed with acetonitrile, and dried in a vacuum oven to provide 1.1 g of *N*-{4-[4-amino-2-(2-hydroxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}methanesulfonamide, mp 206-208 °C. Anal calcd for $C_{17}H_{23}N_5O_3S$: %C, 54.09; %H, 6.14; %N, 18.55. Found: %C, 53.83; %H, 6.29; %N, 18.29.

Example 4

1-(2-Amino-2-methylpropyl)-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

Under a nitrogen atmosphere, triethylamine (6.6 mL, 47 mmol) was added slowly to a solution of 2,4-dichloro-3-nitroquinoline (10.0 g, 41.1 mmol) in anhydrous 1-methyl-2-pyrrolidinone (40 mL). The reaction mixture was cooled to 0 °C with an ice bath. A solution of 1,2-diamino-2-methylpropane (4.1 g, 47.3 mmol) in anhydrous 1-methyl-2-pyrrolidinone (5 mL) was added dropwise over a period of 15 minutes while maintaining the temperature of the reaction mixture below 4 °C. After the addition was completed the

ice bath was removed and the reaction mixture was allowed to stir at ambient temperature for 4 hours. The reaction mixture was slowly poured into vigorously stirred warm water (300 mL). The resulting suspension was stirred for 1 hour and then cooled to 13 °C by adding ice. The solid was isolated by filtration and then washed with cold water until the filtrate was clear to provide 12.1 g of N^1-(2-chloro-3-nitroquinolin-4-yl)-2-methylpropane-1,2-diamine as a damp yellow solid.

Part B

A solution of sodium hydroxide (1.8 g of solid sodium hydroxide dissolved in 45 mL of water) was added slowly to a solution of the material from Part A (41.1 mmol) in tetrahydrofuran (96 mL). A solution of di-*tert*-butyl dicarbonate (10.8 g, 49.4 mmol) in tetrahydrofuran (30 mL) was added dropwise over a period of 15 minutes. The reaction solution was stirred at ambient temperature. After 6 hours 10% sodium hydroxide (2 mL) and additional di-*tert*-butyl dicarbonate (1.5 g) were added and the reaction solution was stirred at ambient temperature overnight. The layers were separated and the tetrahydrofuran was removed under reduced pressure to provide a mixture. The mixture was diluted with water (200 mL) and then extracted with dichloromethane (2 x 100 mL). The organics were combined, washed sequentially with aqueous sodium carbonate (2 x 150 mL) and brine (100 mL), dried over sodium sulfate and magnesium sulfate, filtered, and then concentrated under reduced pressure. The residue was triturated with heptane (75 mL) for 15 minutes at 65 °C and then filtered while hot. The isolated solids were washed with heptane (20 mL) to provide 13.2 g of *tert*-butyl *N*-{2-[(2-chloro-3-nitroquinolin-4-yl)amino]-1,1-dimethylethyl}carbamate as a yellow powdery solid.

Part C

A Parr vessel was charged with 5% Pt/C (0.5 g) and acetonitrile (10 mL). A solution of the material from Part B in acetonitrile (450 mL) was added. The vessel was placed on a Parr shaker under hydrogen pressure (40 psi, 2.8 x 10^5 Pa) for 5 hours. The reaction mixture was filtered through a layer of CELITE filter aid to remove the catalyst. The filtrate was carried on to the next step.

Part D

The solution of *tert*-butyl *N*-{2-[(3-amino-2-chloroquinolin-4-yl)amino]-1,1-dimethylethyl}carbamate in acetonitrile from Part C was cooled to 5 °C using an ice bath. A solution of acetoxyacetyl chloride (4.8 g, 35.1 mmol) in acetonitrile (20 mL) was added

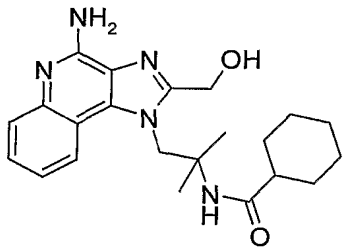
dropwise at a rate such that the temperature of the reaction mixture was maintained at 5 °C. After the addition was complete the ice bath was removed and the reaction mixture was allowed to stir at ambient temperature for 5 hours. The reaction mixture was concentrated under reduced pressure to provide 16.7 g of *N*-{2-[(3-acetoxyacetylamino-2-chloroquinolin-4-yl)amino]-1,1-dimethylethyl}carbamate hydrochloride as a yellow powder.

Part E

A mixture of the material from Part D (15.7 g) and ammonia in methanol (235 mL of 7 N) was divided into equal portions and placed in pressure vessels. The vessels were sealed, heated at 160 °C for 20 hrs, and then allowed to cool to ambient temperature overnight. The reaction mixtures were filtered. The isolated solids were washed with water and dried in a vacuum oven at 60 °C overnight to provide 6.0 g of a tan powder. A portion (1 g) was treated with activated charcoal and recrystallized from ethanol (75 mL) to provide 0.5 g of 1-(2-amino-2-methylpropyl)-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white granular solid, mp 248-250 °C. Anal calcd for $C_{15}H_{19}N_5O$: %C, 63.14; %H, 6.71; %N, 24.54. Found: %C, 63.13; %H, 6.81; %N, 24.64.

Example 5

N-[2-(4-Amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]cyclohexanecarboxamide



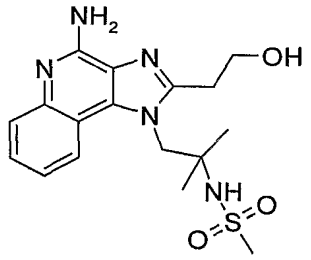
A solution of 1-(2-amino-2-methylpropyl)-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (2.0 g, 7.0 mmol) in 1-methyl-2-pyrrolidinone (30 mL) was cooled to -20 °C. Triethylamine (1.1 mL, 7.7 mmol) was added in a single portion. A chilled (-5 °C) solution of cyclohexanecarbonyl chloride (1.03 g, 7.0 mmol) in 1-methyl-2-pyrrolidinone (2 mL) was added dropwise over a period of 20 minutes while maintaining the reaction mixture at -20 °C. The reaction mixture was stirred at ambient temperature overnight. Additional cyclohexanecarbonyl chloride (0.1 g) was added and the reaction

mixture stirred for 2 hours. The reaction mixture was poured into water with vigorous stirring. The resulting precipitate was isolated by filtration to provide 1.7 g of an ivory powder. Analysis by high performance liquid chromatography and NMR indicated that the powder was a mixture of the desired product and an ester formed from the reaction of the hydroxy group of the desired product with cyclohexanecarbonyl chloride.

The powder was dissolved in ethanol (25 mL), combined with a solution of sodium hydroxide (0.21 g) in water (25 mL), and then heated at 50 °C for 3 hours. The ethanol was removed under reduced pressure and the solids were isolated by filtration to provide 1.2 g of a light tan powder. The powder was dissolved in a mixture of acetonitrile (100 mL), water (2 mL) and ethanol (25 mL). The solution was allowed to stand overnight and was then concentrated to a volume of 5 mL to provide a white paste. The paste was triturated with warm (70 °C) acetonitrile (50 mL) for 30 minutes, heated to reflux, and then allowed to cool to ambient temperature. The resulting solid was isolated by filtration to provide 1.05 g of *N*-[2-(4-amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]cyclohexanecarboxamide as a light yellow powder, mp 248-250 °C. Anal calcd for $C_{22}H_{29}N_5O_2$: %C, 66.81; %H, 7.39; %N, 17.71; Found: %C, 66.56; %H, 7.60; %N, 17.82.

Example 6

N-{2-[4-Amino-2-(2-hydroxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1,1-dimethylethyl}methanesulfonamide



Part A

Triethylamine (39.3 mL, 0.282 mol) was added to a chilled (ice bath) solution of N^1-(2-chloro-3-nitroquinolin-4-yl)-2-methylpropane-1,2-diamine (41.42 g, 0.141 mol) in dichloromethane (about 500 mL). Under a nitrogen atmosphere a solution of methanesulfonic anhydride in (29.47 g, 0.169 mol) in dichloromethane (100 mL) was added via a cannula to the reaction mixture over a period of 45 minutes. After the addition

was complete the ice bath was removed and the reaction mixture was allowed to stir at ambient temperature overnight. The reaction mixture was washed sequentially with saturated aqueous sodium bicarbonate (x2) and brine, dried over a mixture of sodium sulfate and magnesium sulfate, filtered, and then concentrated under reduced pressure to provide 46.22 g of an orange solid. This material was recrystallized from toluene (about 1 L), isolated by filtration, rinsed with cold toluene, and dried under high vacuum at 60 °C to provide 33.09 g of *N*-{2-[(2-chloro-3-nitroquinolin-4-yl)amino]-1,1-dimethylethyl}methanesulfonamide.

Part B

A hydrogenation vessel was charged with 5% Pt/C (4.14 g) and a solution of *N*-{2-[(2-chloro-3-nitroquinolin-4-yl)amino]-1,1-dimethylethyl}methanesulfonamide (54.59 g, 0.147 mol) in acetonitrile (1800 mL). The vessel was placed under hydrogen pressure (48 psi, 3.3 x 10^5 Pa) overnight. An additional portion (4.25 g) of catalyst was added and the vessel was placed under hydrogen pressure (48 psi, 3.3 x 10^5 Pa) for 4 hours. The reaction mixture was filtered through a layer of CELITE filter aid and the filter cake was rinsed with fresh acetonitrile until the washes were clear.

Part C

Under a nitrogen atmosphere, 3-methoxypropionyl chloride (17.6 mL, 0.162 mol) was added dropwise to the solution of *N*-{2-[(3-amino-2-chloroquinolin-4-yl)amino]-1,1-dimethylethyl}methanesulfonamide (0.147 mol) in acetonitrile (2.2 L) from Part B. The reaction mixture was allowed to stir at ambient temperature over the weekend. The resulting precipitate was isolated by filtration, rinsed with a small amount of acetonitrile, and then dried under high vacuum at 60 °C to provide 55.84 g of *N*-{2-chloro-4-[2-(methanesulfonylamino)-2-methylpropyl]quinolin-3-yl}-3-methoxypropionamide.

Part D

A Parr bomb was charged with 25.0 g of *N*-{2-chloro-4-[2-(methanesulfonylamino)-2-methylpropyl]aminoquinolin-3-yl}-3-methoxypropionamide and ammonia in methanol (300 mL of 7 N). A second vessel was charged with 30.21 g of *N*-{2-chloro-4-[2-(methanesulfonylamino)-2-methylpropyl]quinolin-3-yl}-3-methoxypropionamide and ammonia in methanol (400 mL of 7 N). Both vessels were sealed and then heated at 170 °C for 14 hours. The reaction mixtures were combined and the solvent was removed under reduced pressure. The residue was partitioned between

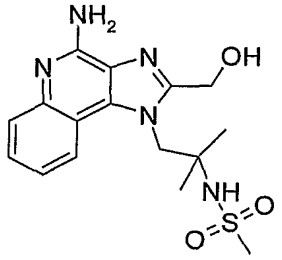
dichloromethane and saturated aqueous sodium bicarbonate. The organic layer was washed sequentially with saturated aqueous sodium bicarbonate and brine, dried over sodium sulfate, filtered, and then concentrated under reduced pressure to provide 38.16 g of *N*-{2-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1,1-dimethylethyl}methanesulfonamide as an off white foam.

Part E

Under a nitrogen atmosphere, boron tribromide (3.5 mL of 1 M in dichloromethane) was added dropwise to a chilled (0 °C) solution of *N*-{2-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1,1-dimethylethyl}methanesulfonamide (0.55 g, 1.40 mmol) in dichloromethane (20 mL). The reaction was allowed to warm to ambient temperature overnight. The reaction was quenched with methanol (10 mL) and the solvent was removed under reduced pressure. The residue was dissolved in hydrochloric acid (6 N), stirred at 50 °C for about 2.5 hours, and then allowed to cool to ambient temperature. The reaction mixture was adjusted to pH 11 with ammonium hydroxide and then extracted with dichloromethane (x 10). The combined organics were washed with brine, dried over sodium sulfate, filtered, and then concentrated under reduced pressure to provide 0.47 g of a white solid. This material was purified by prep HPLC (HORIZON HPFC system, eluting with a gradient of 30-50% CMA in chloroform for 15 column volumes followed by 50% CMA in chloroform for 5 column volumes) and then dried under high vacuum to provide 250 mg of *N*-{2-[4-amino-2-(2-hydroxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1,1-dimethylethyl}methanesulfonamide as white solid, m.p. 209 - 212°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.30 (d, J = 8.2 Hz, 1H), 7.60 (d, J = 8.2 Hz, 1H), 7.39 (m, 1H), 7.27 (s, 1H), 7.21 (m, 1H), 6.49 (s, 2H), 4.84 (t, J = 5.4 Hz, 2H), 4.82 (br s, 1H), 3.88 (m, 2H), 3.18 (br s, 2H), 3.00 (s, 3H), 1.27 (br s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 153.6, 152.0, 145.4, 133.5, 126.9, 126.8, 126.5, 121.3, 120.8, 115.6, 60.5, 57.9, 54.1, 44.8, 31.4, 25.8; MS (ESI) *m/z* 378 $(M + H)^+$; Anal. calcd for $C_{17}H_{23}N_5O_3S$: %C, 54.09; %H, 6.14; %N, 18.55. Found: %C, 53.76; %H, 6.02; %N, 18.32.

Example 7

N-[2-(4-Amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]methanesulfonamide



Part A

A pressure vessel was charged with a solution of of *N*-{2-[(2-chloro-3-nitroquinolin-4-yl)amino]-1,1-dimethylethyl}methanesulfonamide (5 g, 13 mmol) in acetonitrile (150 mL). Catalyst was added (0.5 g of 5% Pt/C) and the vessel was placed under hydrogen pressure (50 psi, 3.4 X 10^5 Pa) for 2 hours. The reaction mixture was filtered through a layer of CELITE filter aid.

Part B

The solution of *N*-{2-[(3-amino-2-chloroquinolin-4-yl)amino]-1,1-dimethylethyl}methanesulfonamide in acetonitrile from Part A was chilled in an ice bath. Acetoxyacetyl chloride (1.5 mL, 14 mmol) was added over a period of 5 minutes. The reaction mixture was allowed to stir for 3 hours. A precipitate was isolated by filtration and rinsed with acetonitrile to provide crude *N*-{2-chloro-4-[2-(methanesulfonylamino)-2-methylpropyl]quinolin-3-yl}acetoxyacetamide hydrochloride.

Part C

A solution of sodium hydroxide (0.8 g) in water (15 mL) was added to a suspension of the material from Part B in ethanol (60 mL) until all of the solid dissolved. The reaction mixture was heated at 60 °C overnight and then concentrated under reduced pressure. The residue was dissolved in water (50 mL), sodium chloride (10 g) was added, and the mixture was extracted with chloroform (3 x 300 mL). The extracts were concentrated under reduced pressure to provide about 4 g of crude *N*-[2-(4-chloro-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]methanesulfonamide.

Part D

The material from Part C was combined with a solution of ammonia in methanol (50 mL of 7 N) and heated at 150 °C for 10 hours. The reaction mixture was allowed to

cool to ambient temperature. A precipitate was isolated by filtration, rinsed with methanol (20 mL), slurried with water (50 mL), isolated by filtration, washed with water (20 mL), and dried to provide 2.7 g of a brown crystalline solid. This material was combined with methanol (50 mL), heated at 50 °C overnight, and then isolated by filtration to provide 2.3 g of *N*-[2-(4-amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]methanesulfonamide, mp 262-265 °C. Anal. calcd for $C_{16}H_{21}N_5O_3S$: %C, 52.88; %H, 5.82; %N, 19.27. Found: %C, 52.64; %H, 5.95; %N, 19.50.

Examples 8 – 72

Part A

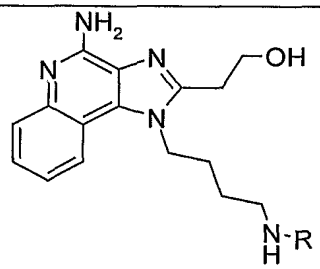
A reagent (1.1 eq) from Table 1 below was added to a test tube containing a solution of 1-(4-aminobutyl)-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (73 mg) in *N,N*-dimethylacetamide (1 mL) containing *N,N*-diisopropylethylamine (2 eq). The test tube was placed on a shaker overnight. The solvent was removed by vacuum centrifugation. The reaction mixtures were separated by solid-supported liquid-liquid extraction according to the following procedure. Each sample was dissolved in chloroform (1 mL) then loaded onto diatomaceous earth that had been equilibrated with de-ionized water (600 µL) for about 20 minutes. After 10 minutes chloroform (500 µL) was added to elute the product from the diatomaceous earth into a well of a collection plate. After an additional 10 minutes the process was repeated with additional chloroform (500 µL). The solvent was then removed by vacuum centrifugation.

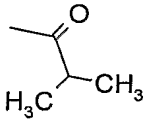
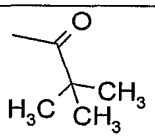
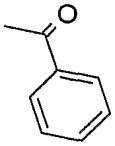
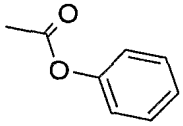
Part B

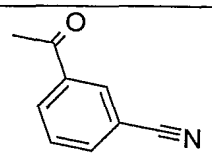
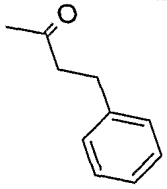
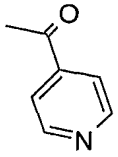
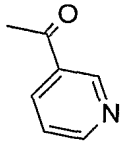
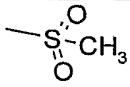
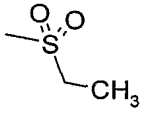
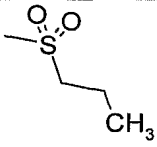
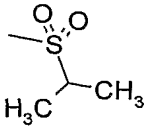
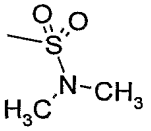
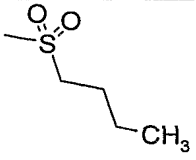
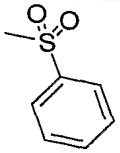
The residue (in a test tube) was combined with dichloromethane (1 mL) and the mixture was sonicated to dissolve the solids. The solution was cooled (0 °C) and then combined with boron tribromide (400 µL of 1 M in heptane). The mixture was shaken for 5 minutes, placed in an ice bath for 30 minutes, and then shaken overnight. The solvents were removed by vacuum centrifugation. The residue was diluted with methanol (1 mL) and hydrochloric acid (500 µL of 6 N). The mixture was shaken for 30 minutes and then the solvents were removed by vacuum centrifugation. The compounds were purified by preparative high performance liquid chromatography (prep HPLC) using a Waters FractionLynx automated purification system. The prep HPLC fractions were analyzed using a Waters LC/TOF-MS, and the appropriate fractions were centrifuge evaporated to

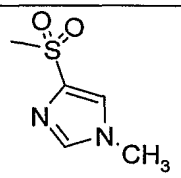
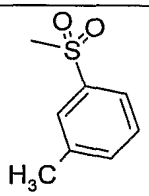
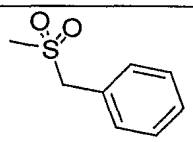
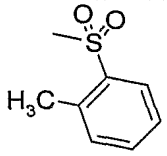
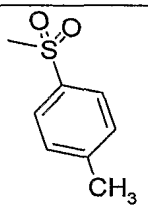
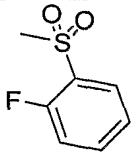
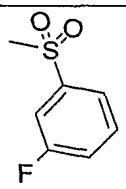
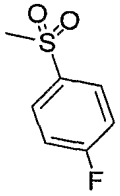
provide the trifluoroacetate salt of the desired compound. Reversed phase preparative liquid chromatography was performed with non-linear gradient elution from 5-95% B where A is 0.05% trifluoroacetic acid/water and B is 0.05% trifluoroacetic acid/acetonitrile. Fractions were collected by mass-selective triggering. Table 1 below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

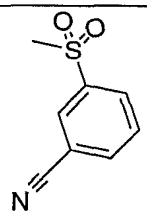
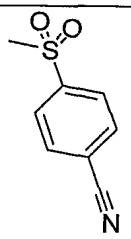
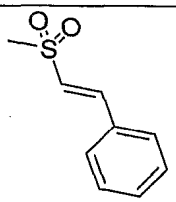
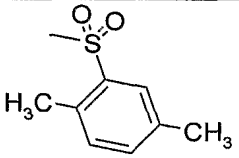
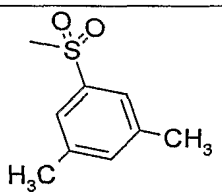
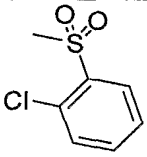
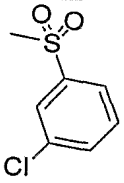
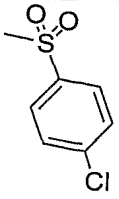
Table 1

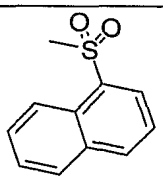
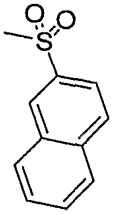
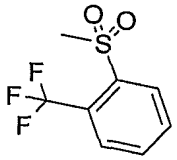
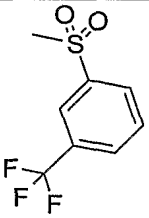
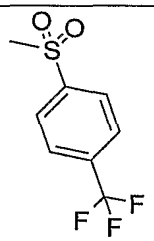
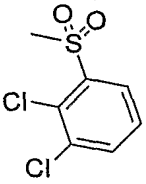
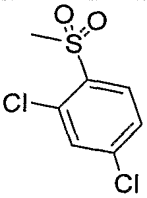
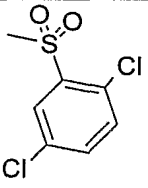


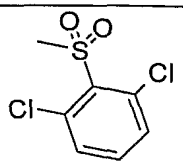
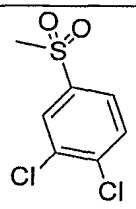
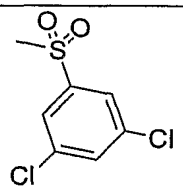
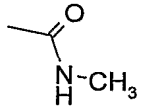
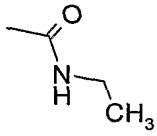
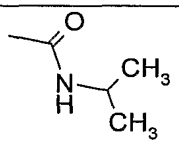
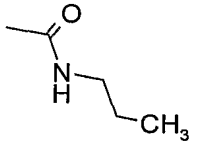
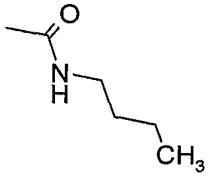
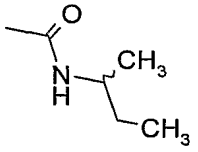
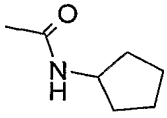
Example	Reagent	R	Measured Mass (M+H)
8	None		300.1840
9	Cyclopropanecarbonyl chloride		368.2063
10	Isobutyryl chloride		370.2224
11	Pivaloyl chloride		384.2390
12	Benzoyl chloride		404.2103
13	Phenyl chloroformate		420.2056

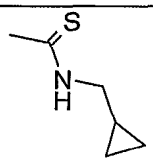
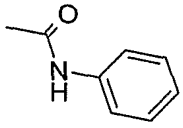
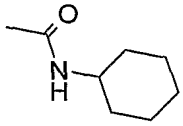
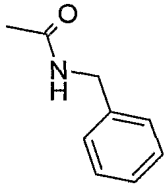
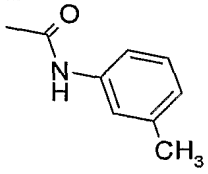
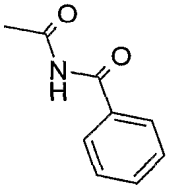
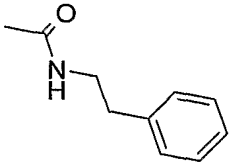
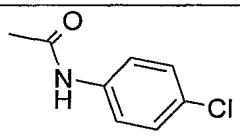
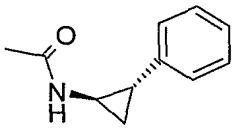
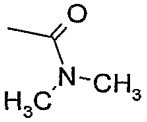
14	3-Cyanobenzoyl chloride		429.2031
15	Hydrocinnamoyl chloride		432.2377
16	Isonicotinoyl chloride hydrochloride		405.2071
17	Nicotinoyl chloride hydrochloride		405.2058
18	Methanesulfonyl chloride		378.1592
19	Ethanesulfonyl chloride		392.1729
20	1-Propanesulfonyl chloride		406.1899
21	Isopropylsulfonyl chloride		406.1888
22	Dimethylsulfamoyl chloride		407.1853
23	1-Butanesulfonyl chloride		420.2050
24	Benzenesulfonyl chloride		440.1741

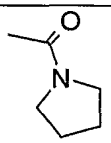
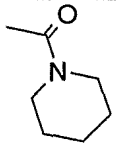
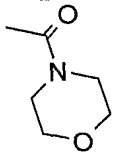
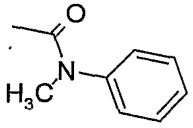
25	1-Methylimidazole-4-sulfonyl chloride		444.1806
26	3-Methylbenzenesulfonyl chloride		454.1895
27	*alpha*-Toluenesulfonyl chloride		454.1923
28	o-Toluenesulfonyl chloride		454.1944
29	*p*-Toluenesulfonyl chloride		454.1907
30	2-Fluorobenzenesulfonyl chloride		458.1664
31	3-Fluorobenzenesulfonyl chloride		458.1652
32	4-Fluorobenzenesulfonyl chloride		458.1639

33	3-Cyanobenzenesulfonyl chloride		465.1678
34	4-Cyanobenzenesulfonyl chloride		465.1668
35	*beta*-Styrene sulfonyl chloride		466.1895
36	2,5-Dimethylbenzenesulfonyl chloride		468.2063
37	3,5-Dimethylbenzenesulfonyl chloride		468.2046
38	2-Chlorobenzenesulfonyl chloride		474.1351
39	3-Chlorobenzenesulfonyl chloride		474.1385
40	4-Chlorobenzenesulfonyl chloride		474.1390

41	1-Naphthalenesulfonyl chloride		490.1891
42	2-Naphthalenesulfonyl chloride		490.1885
43	2-(Trifluoromethyl)benzenesulfonyl chloride		508.1592
44	3-(Trifluoromethyl)benzenesulfonyl chloride		508.1612
45	4-(Trifluoromethyl)benzenesulfonyl chloride		508.1640
46	2,3-Dichlorobenzenesulfonyl chloride		508.0967
47	2,4-Dichlorobenzenesulfonyl chloride		508.0979
48	2,5-Dichlorobenzenesulfonyl chloride		508.0987

49	2,6-Dichlorobenzenesulfonyl chloride		508.0968
50	3,4-Dichlorobenzenesulfonyl chloride		508.0961
51	3,5-Dichlorobenzenesulfonyl chloride		508.0985
52	Methyl isocyanate		357.2073
53	Ethyl isocyanate		371.2203
54	Isopropyl isocyanate		385.2347
55	*n*-Propyl isocyanate		385.2349
56	*n*-Butyl isocyanate		399.2494
57	*sec*-Butyl isocyanate		399.2517
58	Cyclopentyl isocyanate		411.2516

59	Cyclopropylmethyl isothiocyanate		413.2133
60	Phenyl isocyanate		419.2226
61	Cyclohexyl isocyanate		425.2701
62	Benzyl isocyanate		433.2374
63	*m*-Tolyl isocyanate		433.2344
64	Benzoyl isocyanate		447.2126
65	2-Phenyl ethylisocyanate		447.2512
66	4-Chlorophenyl isocyanate		453.1797
67	*trans*-2-Phenylcyclopropyl isocyanate		459.2518
68	*N*,*N*-Dimethylcarbamoyl chloride		371.2185

69	1-Pyrrolidinecarbonyl chloride		397.2382
70	1-Piperidinecarbonyl chloride		411.2526
71	4-Morpholinylcarbonyl chloride		413.2330
72	*N*-Methyl-*N*-phenylcarbamoyl chloride		433.2364

Examples 73 – 110

Part A

Tert-Butyl 3-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propylcarbamate (5 g, U.S. Patent No. 6,573,273, example 148) and hydrochloric acid in dioxane (100 mL of 4 M) were combined and stirred for 4 hours at ambient temperature. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in methanol (30 mL). The pH was adjusted to pH 8 with 6 M sodium hydroxide. The solution was diluted with dichloromethane, ethyl acetate, triethylamine, and brine. The organic layer was concentrated under reduced pressure to provide an orange solid. This material was purified by prep HPLC (COMBIFLASH system eluting first with a gradient of 0 to 10% methanol in dichloromethane containing 1% ammonium hydroxide and then with a gradient of 9 to 30% methanol in dichloromethane containing 1% ammonium hydroxide) to provide 1.58 g of 1-(3-aminopropyl)-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a yellow solid.

Part B

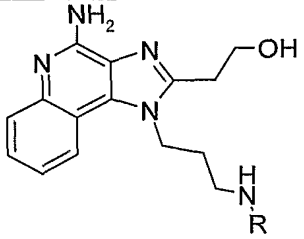
A reagent (1.1 eq) from Table 2 below was added to a test tube containing a solution of 1-(3-aminopropyl)-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (30 mg) in chloroform (1 mL) containing *N,N*-diisopropylethylamine (1.5 eq). The test tube was placed on a shaker overnight. The reaction mixtures were separated by solid-

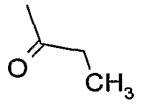
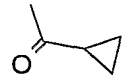
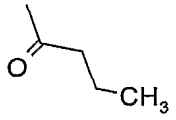
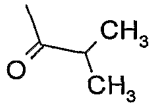
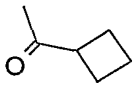
supported liquid-liquid extraction according to the following procedure. Each reaction mixture was loaded onto diatomaceous earth that had been equilibrated with de-ionized water (600 μL) for about 20 minutes. After 10 minutes chloroform (500 μL) was added to elute the product from the diatomaceous earth into a well of a collection plate. After an additional 10 minutes the process was repeated with additional chloroform (500 μL). The solvent was then removed by vacuum centrifugation.

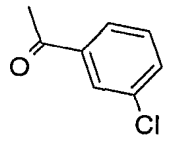
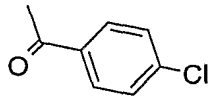
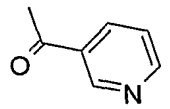
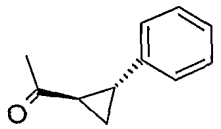
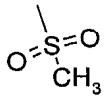
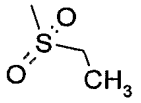
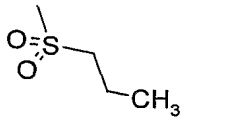
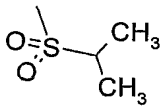
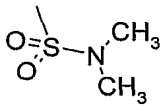
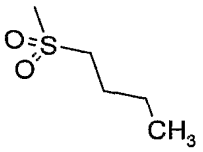
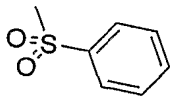
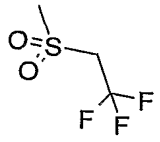
Part C

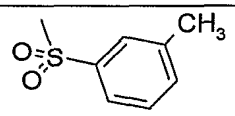
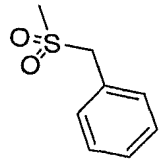
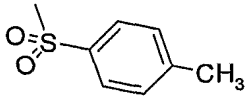
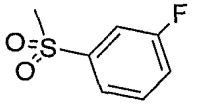
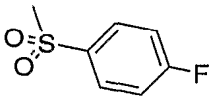
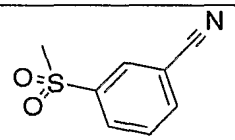
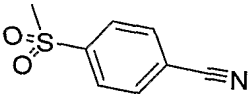
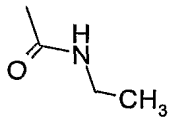
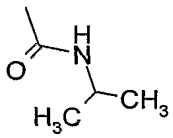
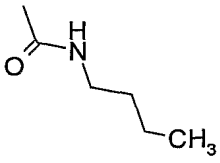
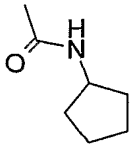
The ether was cleaved and the resulting product was purified using the method of Part B in Examples 8 – 72. Table 2 below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

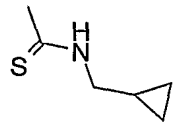
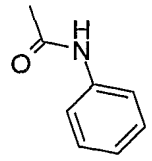
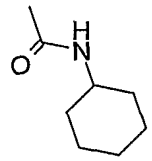
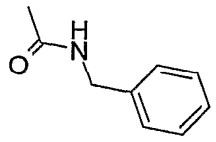
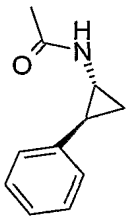
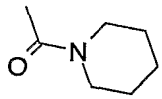
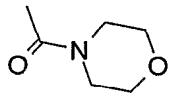
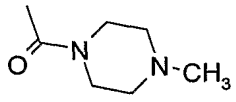
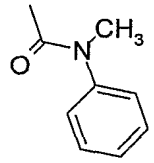
Table 2



Example	Reagent	R	Measured Mass (M+H)
73	None		286.1689
74	Propionyl chloride		342.1956
75	Cyclopropanecarbonyl chloride		354.1946
76	Butyryl chloride		356.2122
77	Isobutyryl chloride		356.2119
78	Cyclobutanecarbonyl chloride		368.2120

79	3-Chlorobenzoyl chloride		424.1570
80	4-Chlorobenzoyl chloride		424.1583
81	Nicotinoyl chloride hydrochloride		391.1913
82	*trans*-2-Phenyl-1-cyclopropanecarbonyl chloride		430.2257
83	Methanesulfonyl chloride		364.1479
84	Ethanesulfonyl chloride		378.1639
85	1-Propanesulfonyl chloride		392.1783
86	Isopropylsulfonyl chloride		392.1788
87	Dimethylsulfamoyl chloride		393.1715
88	1-Butanesulfonyl chloride		406.1946
89	Benzenesulfonyl chloride		426.1633
90	2,2,2-Trifluoroethanesulfonyl chloride		432.1355

91	3-Methylbenzenesulfonyl chloride		440.1774
92	*alpha*-Toluenesulfonyl chloride		440.1762
93	*p*- Toluenesulfonyl chloride		440.1790
94	3-Fluorobenzenesulfonyl chloride		444.1523
95	4-Fluorobenzenesulfonyl chloride		444.1545
96	3-Cyanobenzenesulfonyl chloride		451.1554
97	4-Cyanobenzenesulfonyl chloride		451.1582
98	Ethyl isocyanate		357.2050
99	Isopropyl isocyanate		371.2234
100	*n*-Butyl isocyanate		385.2364
101	Cyclopentyl isocyanate		397.2359

102	Cyclopropylmethyl isothiocyanate		399.1979
103	Phenyl isocyanate		405.2040
104	Cyclohexyl isocyanate		411.2526
105	Benzyl isocyanate		419.2239
106	*trans*-2-Phenylcyclopropyl isocyanate		445.2388
107	1-Piperidinecarbonyl chloride		397.2384
108	4-Morpholinylcarbonyl chloride		399.2173
109	4-Methyl-1-piperazinecarbonyl chloride		412.2485
110	*N*-Methyl-*N*-phenylcarbamoyl chloride		419.2229

Examples 111 – 140

Boron tribromide (400 μL of 1 M in heptane) was added to a tube containing a chilled (0 °C) solution of a compound of Formula Xa (about 25 mg) in dichloromethane (1 mL). The tube was vortexed, maintained at 0 °C for 0.5 hour, and then shaken overnight

at ambient temperature. The reaction mixture was diluted with methanol (1 mL) and hydrochloric acid (250 μL of 6 N), vortexed, and then the solvents were removed by vacuum centrifugation. The compounds were purified by prep HPLC as described in Examples 8 – 72. Table 3 shows the structure of the starting material, a reference for the starting material, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

Table 3

Xa Ia

Example	Reference Formula III	R_1	Measured Mass (M+H)
111	U.S. Patent No. 6,756,382 Example 57		455.2222
112	U.S. Patent No. 6,331,539 Example 121		458.1657

113	U.S. Patent No. 6,331,539 Example 111		378.1599
114	Example 3 Part C		300.1853
115	U.S. Patent No. 6,541,485 Example 121		413.2301
116	U.S. Patent No. 6,756,382 Example 182		455.2198

117	U.S. Patent No. 6,756,382 Example 183		456.2161
118	U.S. Patent No. 6,573,273 Example 145		475.2829
119	U.S. Patent No. 6,677,349 Example 243		434.2253
120	Example 73 Part A		286.1683

121	U.S. Patent No. 6,756,382 Example 187		460.2737
122	U.S. Patent No. 6,677,349 Example 247		364.1446
123	U.S. Patent No. 6,573,273 Example 158		411.2505
124	U.S. Patent No. 6,756,382 Example 190		418.2275

125	U.S. Patent No. 6,664,264 Example 16		377.1655
126	U.S. Patent No. 6,573,273 Example 162		385.2358
127	U.S. Patent No. 6,677,349 Example 253		440.1720
128	U.S. Patent No. 6,573,273 Example 163		399.2145
129	U.S. Patent No. 6,677,349[#]		314.1980

130	U.S. Patent No. 6,573,273 Example 169		433.2321
131	U.S. Patent No. 6,677,349 Example 256		392.1757
132	U.S. Patent No. 6,756,382 Example 196		390.1929
133	U.S. Patent No. 6,683,088 Example 3		408.1714

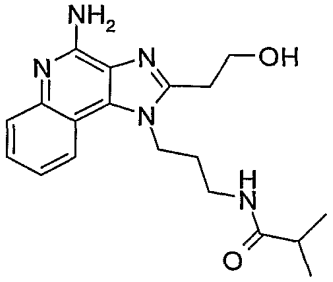
134	U.S. Patent No. 6,664,265 Example 8		434.2197
135	U.S. Patent No. 6,664,265 Example 73		440.2672
136	U.S. Patent No. 6,677,349#		350.1316
137	U.S. Patent No. 6,573,273#		343.1884
138	U.S. Patent No. 6,451,810#		356.2078

139	U.S. Patent No. 6,677,349#		378.1595
140	U.S. Patent Publication 2004/0091491 IRM3		554.4064

#Although not specifically exemplified the compound can be readily prepared using the disclosed synthetic routes.

Example 141

N-{3-[4-Amino-2-(2-hydroxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}-2-methylpropionamide



Part A

1-(3-Aminopropyl)-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine dihydrochloride (6 g, 16 mmol) was combined with triethylamine (11.2 mL, 80 mmol) and pyridine (100 mL). Isobutyryl chloride (1.9 g, 18 mmol) was added dropwise and the reaction mixture was stirred at ambient temperature for 1 hour. The reaction mixture was combined with saturated aqueous sodium bicarbonate and extracted with dichloromethane (3 x 200 mL). The combined organics were dried over magnesium sulfate, filtered through a layer of CELITE filter aid, and then concentrated under reduced pressure to provide 6.2 g of crude *N*-{3-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}-2-methylpropionamide as a brown solid.

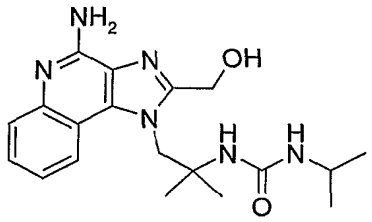
Part B

The material from Part A was combined with dichloromethane (40 mL), stirred until homogeneous, and then chilled in an ice bath. Boron tribromide (40 mL of 1 M in dichloromethane) was slowly added. The ice bath was removed and the reaction mixture was stirred overnight at ambient temperature. The reaction mixture was concentrated under reduced pressure. The residue was combined with methanol (50 mL) and hydrochloric acid (50 mL of 6 N) and heated at 50 °C for 2 hours. The solution was adjusted to pH 9 with sodium hydroxide (6 M) and then extracted first with ethyl acetate (3 x 100 mL) and then with dichloromethane. The organics were dried over magnesium sulfate, filtered through a layer of CELITE filter aid, and then concentrated under reduced pressure. The residue was purified by prep HPLC (HORIZON HPFC system, eluting with a gradient of 0-10% methanol in dichloromethane), recrystallized from acetonitrile, and then dried in a vacuum oven to provide 208 mg of *N*-{3-[4-amino-2-(2-hydroxyethyl)-1*H*-

imidazo[4,5-*c*]quinolin-1-yl]propyl}-2-methylpropionamide as an off-white solid, mp 196-198 °C. Anal. calcd for $C_{19}H_{25}N_5O_2$: %C, 64.20; %H, 7.09; %N, 19.70; Found: %C, 63.99; %H, 7.28; %N, 19.63.

Example 142

1-[2-(4-Amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]-3-(1-methylethyl)urea



Part A

Under a nitrogen atmosphere, a solution of 1,2-diamino-2-methylpropane (52.20 mL, 503.3 mmol), triethylamine (131.8 mL, 958.8 mmol), and dichloromethane (1.0 L) was chilled in an ice water bath. 4-Chloro-3-nitroquinoline (100.0 g, 479.4 mmol) was added in portions over a period of 5 minutes. The reaction mixture was stirred at 0 °C for 2 hours and then allowed to slowly warm to ambient temperature. After 16 hours the reaction mixture was concentrated under reduced pressure. The residue was triturated with water (500 mL) for 1 hour. The resulting solid was isolated by filtration and dried overnight in a vacuum desiccator to provide 124.6 g of N^1-(3-nitroquinolin-1-yl)-2-methylpropane-1,2-diamine as a yellow crystalline solid.

Part B

Under a nitrogen atmosphere, a suspension of N^1-(3-nitroquinolin-1-yl)-2-methylpropane-1,2-diamine (60.0 g, 231 mmol) in dichloromethane (1.0 L) was chilled in an ice bath. Isopropyl isocyanate (23.8 mL, 242 mmol) was added dropwise over a period of 10 minutes. The reaction was allowed to slowly warm to room temperature. After 17 hours additional isopropyl isocyanate (about 2 mL) was added. After an additional 3 hours more isopropyl isocyanate (1 mL) was added. After 2 more hours the reaction mixture was concentrated under reduced pressure to provide 79.8 g of 1-{1,1-dimethyl-2-[(3-nitroquinolin-1-yl)amino]ethyl}-3-(1-methylethyl)urea as a bright yellow solid.

Part C

A pressure vessel was charged with the material from Part B, 5% Pt/C (4.24 g), and acetonitrile (1.5 L). The mixture was placed under hydrogen pressure for 20 hours and then filtered through a layer of CELITE filter aid. The filter cake was rinsed with additional acetonitrile. The filtrate was concentrated under reduced pressure. The residue was dissolved in toluene (750 mL) and then concentrated under reduced pressure to remove residual water. The toluene concentration was repeated. The residue was dissolved in dichloromethane (about 1 L), concentrated under reduced pressure, and then dried under high vacuum to provide 66.4 g of 1-{1,1-dimethyl-2-[(3-aminoquinolin-1-yl)amino]ethyl}-3-(1-methylethyl)urea as an orange foam.

Part D

Under a nitrogen atmosphere, a solution of 1-{1,1-dimethyl-2-[(3-aminoquinolin-1-yl)amino]ethyl}-3-(1-methylethyl)urea (66.0 g, 209 mmol) and triethylamine (32.1 mL, 230 mmol) in dichloromethane (1.0 L) was chilled in an ice bath. Ethoxyacetyl chloride (23.6 mL, 291 mmol) was added dropwise over a period of 10 minutes. The reaction mixture was allowed to slowly warm to ambient temperature overnight. The reaction mixture was concentrated under reduced pressure. The residue was combined with 1-butanol (800 mL) and triethylamine (87 mL, 627 mmol) and heated at 140 °C for 3 hours. The reaction mixture was cooled to ambient temperature and then concentrated under reduced pressure to provide a light brown foam. This material was purified by column chromatography (silica gel, eluting with 98/2/0.5 chloroform/methanol/ammonium hydroxide) to provide 29.36 g of 1-[2-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]-3-(1-methylethyl)urea as a light yellow foam.

Part E

3-Chloroperoxybenzoic acid (26.33 g of 60%, 91.56 mmol) was added in portions over a period of 5 minutes to a chilled solution of the material from Part D in chloroform (350 mL). The reaction mixture was allowed to slowly warm to ambient temperature. After 2 hours the reaction mixture was chilled in an ice bath and ammonium hydroxide (100 mL) was added with vigorous stirring to homogenize. *Para*-toluenesulfonyl chloride (15.27 g, 80.12 mmol) was added in portions over a period of 10 minutes. The ice bath was removed and the reaction mixture was stirred for 30 minutes. The reaction mixture was diluted with water (100 mL) and chloroform (250 mL). The layers were separated.

The organic layer was washed with 10% sodium carbonate (200 mL) and water (200 mL). The combined aqueous was back extracted with chloroform (100 mL). The combined organics were washed with brine (200 mL), dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide a light brown foam. The foam was purified by column chromatography (silica gel, eluting with 95/5 chloroform/methanol) and then recrystallized from acetonitrile to provide 3.75 g of 1-[2-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]-3-(1-methylethyl)urea as an off white solid.

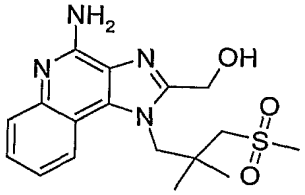
Part F

Under a nitrogen atmosphere, a suspension of 1-[2-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]-3-(1-methylethyl)urea (1.19 g, 2.99 mmol) in dichloromethane (30 mL) was chilled in an ice bath. Boron tribromide (7.47 mL of 1 M in dichloromethane) was added. The reaction mixture was allowed to warm slowly to ambient temperature and then stirred for 18 hours. Additional boron tribromide (2 eq) was added. After 2 hours the reaction mixture was diluted with acetonitrile (10 mL) and the reaction mixture was stirred overnight. The reaction mixture was diluted with dichloromethane (10 mL) and acetonitrile (10 mL), stirred for an additional 16 hours, quenched with methanol (25 mL), and then concentrated under reduced pressure to provide an orange foam. The foam was dissolved in hydrochloric acid (25 mL of 6 N) and heated at 50 °C for 2 hours. The solution was neutralized with 50% sodium hydroxide. The resulting gummy precipitate was extracted with chloroform (3 x 15 mL). The combined organics were washed with brine (15 mL), dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide an off white solid. This material was purified by prep HPLC (HORIZON HPFC system, eluting with a gradient of 15-50% CMA in chloroform) and then recrystallized from acetonitrile to provide 335 g of 1-[2-(4-amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]-3-(1-methylethyl)urea as a white crystalline solid, mp 196–199 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.38 (d, J = 8.0 Hz, 1 H), 7.59 (d, J = 7.5 Hz, 1 H), 7.43-7.38 (m, 1 H), 7.24-7.19 (m, 1 H), 6.54 (s, 2 H), 5.72 (s, 1 H), 5.63 (d, J = 7.6 Hz, 1 H), 5.46 (t, J = 5.7 Hz, 1 H), 5.01 (s, 2 H), 4.78 (s, 2 H), 3.78-3.67 (m, 1 H), 1.17 (bs, 6 H), 1.05 (d, J = 6.9 Hz, 6 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.2, 154.2, 152.3, 145.6, 134.3, 126.8, 126.7, 121.5, 120.9, 115.8, 56.5, 54.2, 52.1, 26.4, 23.6; MS (APCI) *m/z* 371 $(M + H)^+$; Anal.

Calcd for $C_{19}H_{26}N_6O_2 \cdot 0.3H_2O$: %C, 60.72; %H, 7.13; %N, 22.36; Found: %C, 60.44; %H, 7.42; %N, 22.52.

Example 143

{4-Amino-1-[2,2-dimethyl-3-(methylsulfonyl)propyl]-1*H*-imidazo[4,5-*c*]quinolin-2-yl}methanol

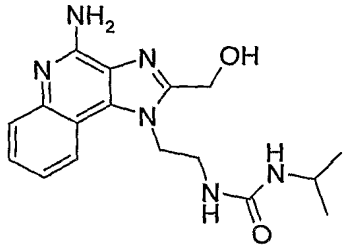


To a suspension of 1-[2,2-dimethyl-3-(methylsulfonyl)propyl]-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (0.4 g, 1.02 mmol) in dichloromethane (5 mL) was added boron tribromide (5.1 mL, 1M solution in dichloromethane). An exotherm was observed upon addition and the mixture turned light purple. After stirring at ambient temperature for 20 hours, the remaining starting material was consumed by adding boron tribromide (2.5 mL, 1M solution in dichloromethane). The reaction was quenched with aqueous hydrochloric acid (1N, 20 mL) to afford a homogeneous mixture. The layers were separated and the aqueous layer washed with dichloromethane (20 mL). The pH of the aqueous layer was adjusted to 12 by addition of aqueous sodium hydroxide (50%) at which time a solid precipitated out of solution. The solid was stirred for 18 hours, collected by filtration and washed with water. The crude product was purified by chromatography over silica gel (eluting with CMA) to afford a white powder. The powder was triturated with methanol (20 mL). The resulting solid was isolated by filtration, washed with methanol and dried for 4 hours at 65 °C to provide 150 mg of {4-amino-1-[2,2-dimethyl-3-(methylsulfonyl)propyl]-1*H*-imidazo[4,5-*c*]quinolin-2-yl}methanol as a white powder, mp 230-232 °C.

Anal. Calcd for $C_{17}H_{22}N_4O_3S$: %C, 56.33; %H, 6.12; %N, 15.46. Found: %C, 56.33; %H, 6.31; %N, 15.27.

Example 144

N-{2-[4-amino-2-(hydroxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}-*N'*-isopropylurea



A stirring solution of *N*-{2-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}-*N'*-isopropylurea (400 mg, 1.1 mmol) in dichloromethane (50 mL) was sealed with a septum and purged with nitrogen gas. The solution was cooled in an ice/water bath and a 1.0 M solution of boron tribromide in dichloromethane (2.2 mL) was added via syringe. The resulting mixture was stirred for 2 hours while warming to ambient temperature. The mixture was cooled back to 0 °C in an ice/water bath and the second portion of boron tribromide (1.0 M, 5.5 mL) was added. The reaction was stirred for 18 hours while warming to ambient temperature. Aqueous hydrochloric acid (6N, 10 ml) was added and the mixture was stirred for 1 hour. The layers were separated and the aqueous fraction was neutralized by the slow addition of solid sodium hydroxide until the pH reached 14. A fine precipitate formed. The aqueous mixture was extracted with chloroform (2x 50 mL) and filtered. The resulting solid (filter cake) was combined with the organic extracts, methanol (50 mL), and silica gel (5 g). The mixture was concentrated under reduced pressure. The crude product absorbed on silica was purified by chromatography using a HORIZON HPFC system (silica cartridge, eluting with 0-35% CMA in chloroform over 2.6 L) followed by recrystallization from acetonitrile to provide 170 mg of *N*-{2-[4-amino-2-(hydroxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}-*N'*-isopropylurea as an off-white solid, mp >240 °C.

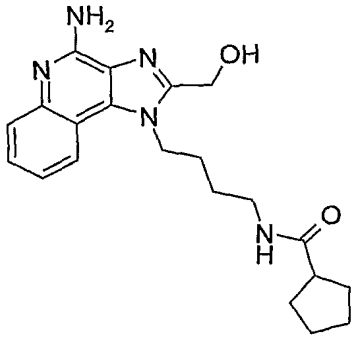
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.30 (d, J = 7.9 Hz, 1H), 7.61 (dd, J = 8.3, 0.9 Hz, 1H), 7.43 (m, 1H), 7.24 (m, 1H), 6.53 (br s, 2H), 5.99 (t, J = 5.8 Hz, 1H), 5.82 (d, J = 7.8 Hz, 1H), 5.67 (d, J = 5.8 Hz, 1H), 4.75 (d, J = 5.8 Hz, 2H), 4.66 (t, J = 6.7 Hz, 2H), 3.69 (m, 1H), 3.48 (q, J = 6.4 Hz, 2H), 1.01 (d, J = 6.5 Hz, 6H);

MS (APCI) *m/z* 343 $(M + H)^+$;

Anal. Calcd. for $C_{17}H_{22}N_6O_2$: %C, 59.63; %H, 6.48; %N, 24.54. Found: %C, 59.64; %H, 6.59; %N, 24.58.

Example 145

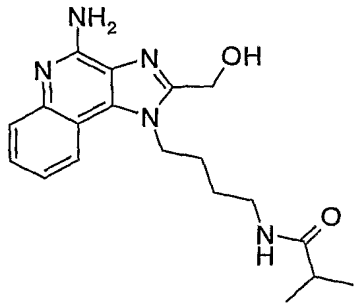
N-{4-[4-amino-2-(hydroxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}cyclopentanecarboxamide



Boron tribromide (2.5 equivalents, 14.6 mL of 1 M solution in dichloromethane) was added dropwise to a cooled (ice bath) suspension of *N*-{4-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}cyclopentanecarboxamide (2.4 g, 5.8 mmol) in dichloromethane (25 mL). The reaction mixture was allowed to slowly warm to ambient temperature and then stirred for 6 days. Additional boron tribromide (5 equivalents, 29 mmol, 29 mL) was added and the reaction was stirred at ambient until starting material was consumed. The reaction was quenched slowly with methanol (100 mL) and then concentrated under reduced pressure. The residue was combined with 6 M hydrochloric acid (100 mL), heated to 50°C, and stirred for 2 hours. The resulting solution was cooled (ice bath) and then free-based (pH 9) with the addition of 6 M aqueous sodium hydroxide. A brown gummy solid formed in the basic aqueous solution. The aqueous liquid was decanted from the solid and acetonitrile was added (30 mL). A white precipitate formed and was isolated by filtration. The white precipitate was then triturated with hot acetonitrile, allowed to cool, isolated by filtration, washed with ether, and dried under vacuum to provide *N*-{4-[4-amino-2-(hydroxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}cyclopentanecarboxamide (0.48 g) as a fine white solid, mp 183-186°C; MS (ESI) *m/z* 382 $(M+H)^+$; Anal. Calcd for $C_{21}H_{27}N_5O_2$: C, 65.35; H, 7.18; N, 18.14; Found C, 65.06; H, 6.90; N, 18.13.

Example 146

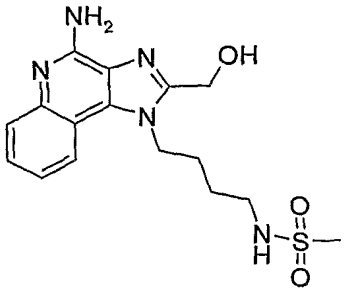
N-[4-(4-amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]isobutyramide



Boron tribromide (2.5 equivalents, 15.6 mL of 1 M solution in dichloromethane) was added dropwise to a cooled (ice bath) suspension of *N*-[4-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-c]quinolin-1-yl)butyl]isobutyramide (2.4 g, 6.2 mmol) in dichloromethane (25 mL). The reaction mixture was allowed to slowly warm to ambient temperature and then stirred for 1 day. Additional boron tribromide (5 equivalents, 31 mmol, 31 mL) was added to the mixture. The reaction was quenched slowly with methanol (100 mL) and then concentrated under reduced pressure. The residue was combined with 6 M hydrochloric acid (100 mL), heated to 50°C, and stirred for 2 hours. The resulting solution was cooled (ice bath) and then free-based (pH 9) with the addition of 6 M sodium hydroxide. A brown gummy solid formed in the basic aqueous solution. The resulting solid was extracted with dichloromethane (6 x 50 mL). The combined extracts were washed with brine (100 mL), dried with magnesium sulfate, filtered, and then concentrated under reduced pressure. This material was purified by prep HPLC (Analogix Separation System, Biotage Si 40+M column, eluted with a gradient of 0-20% methanol in dichloromethane with 1% ammonium hydroxide) to provide a light brown solid. The solid was triturated with hot acetonitrile, allowed to cool, isolated by filtration, washed with ether, and dried under vacuum to provide *N*-[4-(4-amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]isobutyramide (0.049 g) as a white solid, mp 222-224°C; MS (ESI) *m/z* 356 $(M+H)^+$; Anal. Calcd for $C_{19}H_{25}N_5O_2 \cdot 0.25HBr \cdot 0.10H_2O$: C, 60.46; H, 6.80; N, 18.55; Found C, 60.26; H, 6.64; N, 18.43.

Example 147

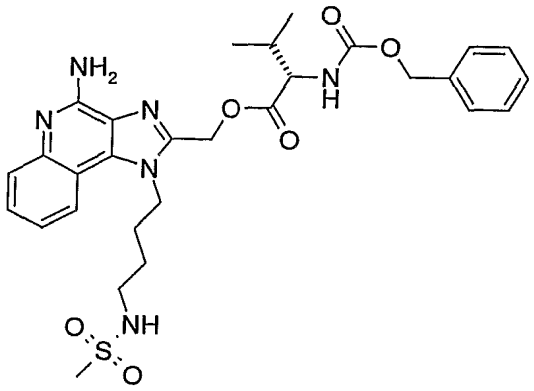
N-[4-(4-amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]methanesulfonamide



Boron tribromide (2.5 equivalents, 20 mL of 1 M solution in dichloromethane) was added dropwise to a cooled (ice bath) suspension of *N*-[4-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]methanesulfonamide (3g, 7.92 mmol) in dichloromethane (20 mL). The reaction mixture was allowed to slowly warm to ambient temperature and then stirred for 4 hours. Additional boron tribromide (2 mL) was added and the mixture was stirred for 3 hours. The reaction was quenched slowly with methanol (20 mL) and then concentrated under reduced pressure. The residue was combined with 6 M hydrochloric acid (50mL), heated to 50°C, and stirred for 2 hours. The resulting solution was concentrated under reduced pressure to a slurry that cooled (ice bath) and then free-based with the addition of 7 M ammonia in methanol (40 mL). The mixture was concentrated under reduced pressure and the addition of 7 M ammonia in methanol (40mL) was repeated 2 more times. The concentrated brown sludge like material was purified by prep HPLC (ISCO Combiflash Separation System, Biotage Si 40+M column, eluted with a gradient of methanol in dichloromethane with 1% ammonium hydroxide) to provide a light brown solid. The solid was triturated with hot acetonitrile, allowed to cool, isolated by filtration, washed with ether, and dried under vacuum to provide *N*-[4-(4-amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]methanesulfonamide (0.1 g) as a fine beige solid, mp 216-219°C; MS (ESI) *m/z* 364 $(M+H)^+$; Anal. Calcd for $C_{16}H_{21}N_5O3S$: C, 52.88; H, 5.82; N, 19.27; Found C, 52.62; H, 5.71; N, 19.02.

Example 148

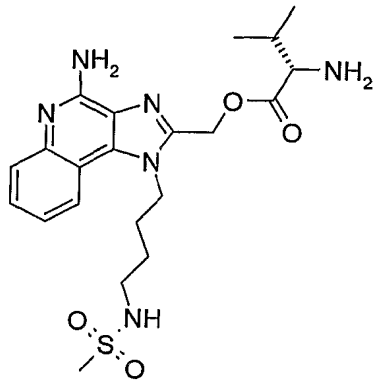
(4-Amino-1-{4-[(methylsulfonyl)amino]butyl}-1*H*-imidazo[4,5-*c*]quinolin-2-yl)methyl *N*-[(benzyloxy)carbonyl]-L-valinate



To a stirred suspension of *N*-[4-(4-amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]methanesulfonamide (2.1 g, 5.8 mmol) in THF was added triphenylphosphine (1.5 equivalents, 8.7 mmol, 2.2 g) followed by CBZ-L-valine (1.5 equivalents, 8.7 mmol, 2.3 g). The suspension was stirred for 5 min after which it was cooled in an ice-bath. To this cooled reaction mixture diisopropyl azodicarboxylate (DIAD,1.8 equivalents, 10.4 mmol, 2.0 mL) was added and the reaction was warmed to room temperature and stirred overnight. The solvent was evaporated under reduced pressure and the crude solid was purified by prep HPLC (ISCO Combiflash Separation System, Biotage Si 40+M column, eluted with a gradient of 0-8% methanol in dichloromethane with 1% ammonium hydroxide) to provide a solid. The solid was heated in diethyl ether and filtered to afford (4-amino-1-{4-[(methylsulfonyl)amino]butyl}-1*H*-imidazo[4,5-*c*]quinolin-2-yl)methyl *N*-[(benzyloxy)carbonyl]-L-valinate (2 g) as a beige solid, mp 99-100°C; MS (ESI) *m/z* 597 $(M+H)^+$; Anal. Calcd for $C_{29}H_{36}N_6O_6S$: C, 58.37; H, 6.08; N, 14.08; Found C, 57.98; H, 6.31; N, 13.82.

Example 149

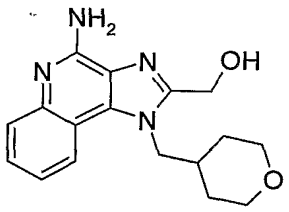
(4-Amino-1-{4-[(methylsulfonyl)amino]butyl}-1*H*-imidazo[4,5-*c*]quinolin-2-yl)methyl L-valinate



To a hydrogenation bottle was added (4-amino-1-{4-[(methylsulfonyl)amino]butyl}-1*H*-imidazo[4,5-*c*]quinolin-2-yl)methyl *N*-[(benzyloxy)carbonyl]-L-valinate (1.5 g, 2.5 mmol) followed by a mixture of methanol (30 mL), THF (15 mL) and water (5 mL) and conc HCl (5 mL). To this was added Pd/C (90 mg) and the reaction was hydrogenated at 40 psi (2.8 X 10^5 Pa) overnight. To the reaction mixture was added conc. HCl (5 mL) and Pd/C (90 mg) and the reaction was hydrogenated at 40 psi (2.8 X 10^5 Pa) for 18 hours. The reaction was filtered through CELITE filter aid and the filtrate was evaporated to afford a clear oil. The product was isolated by prep HPLC (ISCO Combiflash Separation System, Biotage Si 40+M column, eluted with a gradient of 0-8% methanol in dichloromethane with 1% ammonium hydroxide) to provide (4-amino-1-{4-[(methylsulfonyl)amino]butyl}-1*H*-imidazo[4,5-*c*]quinolin-2-yl)methyl L-valinate (0.495 g) as an off white solid, mp 161-163°C; MS (ESI) *m/z* 463 $(M+H)^+$; Anal. Calcd for $C_{21}H_{30}N_6O_4S$: C, 54.53; H, 6.54; N, 18.17; Found C, 53.96; H, 6.62; N, 17.85, delta C = 0.57.

Example 150

[4-Amino-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methanol



Part A

Under a nitrogen atmosphere THF (90 mL) and triethylamine (17.5 mL, 125.6 mmol) were added sequentially to a mixture of crude 4-chloro-3-nitroquinoline (13.10 g,

62.81 mmol) and 1-tetrahydro-2*H*-pyran-4-ylmethylamine hydrochloride (10.0 g, 65.95 mmol). The reaction mixture was placed in an oil bath at 45 °C for 1 hour and then concentrated under reduced pressure. The residue was diluted with THF (30 mL) and water (200 mL). The THF was removed under reduced pressure. A solid was isolated by filtration and dried to provide 16.10 g of 3-nitro-*N*-(tetrahydro-2*H*-pyran-4-ylmethyl)quinolin-4-amine as a light yellow solid.

Part B

A mixture of 3-nitro-*N*-(tetrahydro-2*H*-pyran-4-ylmethyl)quinolin-4-amine (2.50 g), 10% palladium on carbon (0.25 g), and ethanol (40 mL) was placed under hydrogen pressure on a Parr apparatus. When the reaction was complete, the mixture was filtered through a layer of CELITE filter agent. The filter cake was washed with ethanol. The filtrate was concentrated under reduced pressure to provide 2.23 g of N^4-(tetrahydro-2*H*-pyran-4-ylmethyl)quinoline-3,4-diamine as a yellowish-orange oil.

Part C

Chloroacetyl chloride (12 mL, 151 mmol) was dissolved in dichloromethane (30 mL) and added via addition funnel, over 20 minutes, to a stirring solution of N^4-(tetrahydro-2*H*-pyran-4-ylmethyl)quinoline-3,4-diamine (35.3g, 137 mmol) in dichloromethane (300 mL). The resulting solution was stirred at ambient temperature under nitrogen for 24 hours at which point the solution was heated to 40 °C for an additional 24 hours. The mixture was cooled to ambient temperature, diluted with dichloromethane (150 mL) and transferred to a separatory funnel. The organic layer was washed with water (2 x 200 mL) and brine (2 x 200 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure to provide 38.3 g of 2-(chloromethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as a light brown solid.

Part D

3-Chloroperoxybenzoic acid (mCPBA) (3.8 g of 77% pure material, 14.2 mmol) was added to a stirring solution of 2-(chloromethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline (3.0g, 9.50 mmol) in dichloromethane (60 mL). After 15.5 hours, ammonium hydroxide (12 mL) and then *p*-toluenesulfonyl chloride (2.2g, 11.4 mmol) were added to the stirring solution and the biphasic mixture was stirred at ambient temperature for 3 hours. The reaction was diluted with water (50 mL) and then transferred to a separatory funnel. The aqueous layer was extracted with dichloromethane (3 x 100

mL) and the combined organic fractions dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using a HORIZON HPFC system (silica cartridge, eluting with 3 – 20% methanol in dichloromethane) to provide 1.6 g of 2-(chloromethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a yellow solid.

Part E

Potassium acetate (0.41 g, 4.16 mmol) and potassium iodide (0.28g, 1.66 mmol) were added to a stirring solution of 2-(chloromethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (0.55 g, 1.66 mmol) and the resulting suspension was heated to 50 °C. After 17 hours, the suspension was cooled to ambient temperature and concentrated under reduced pressure. The residue was suspended in methanol (10 mL) and water (5 mL) and lithium hydroxide monohydrate (0.35 g, 8.31 mmol) was added in one portion. The resulting solution was stirred at ambient temperature 18 hours and concentrated under reduced pressure. The residue was diluted with water (20 mL) and neutralized with hydrochloric acid (6 N in water). The aqueous layer was extracted with dichloromethane (2 x 50 mL) and ethyl acetate (50 mL). The combined organic fractions were concentrated to a yellow solid which was crystallized from acetonitrile. The crystals were isolated by filtration and dried in a vacuum oven at 65 °C to provide 0.20 g of [4-amino-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methanol as an off-white solid, mp 239-241 °C.

Anal. calcd for $C_{17}H_{20}N_4O_2 \cdot 0.2H_2O$: C, 64.62; H, 6.51; N, 17.73. Found: C, 64.45; H, 6.69; N, 17.62.

Examples 151 – 229

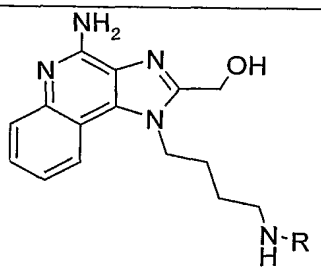
Part A

A solution of 1-(4-aminobutyl)-2-methoxymethyl-1*H*-imidazo[4,5-*c*]quinoline-4-amine (30 mg, 1 eq, prepared according to the general method of Example 3 using methoxyacetyl chloride in lieu of 3-methoxypropionyl chloride) and *N,N*-diisopropylethylamine (2 eq) in *N,N*-dimethylacetamide (1 mL) was added to a tube containing a reagent (1.1 eq) from the table below. The reaction mixture was vortexed overnight and then quenched with water (100 µL). The solvents were removed by vacuum centrifugation. The residue was purified by solid-supported liquid-liquid extraction

according to the following procedure. The sample was dissolved in chloroform (1 mL) then loaded onto diatomaceous earth that had been equilibrated with 1 M sodium hydroxide (600 μL) for about 20 minutes. After 10 minutes chloroform (500 μL) was added to elute the product from the diatomaceous earth into a well of a collection plate. After an additional 10 minutes the process was repeated with additional chloroform (500 μL). The solvent was then removed by vacuum centrifugation.

Part B

The residue (in a test tube) was combined with dichloromethane (500 μL) and the tube was vortexed to dissolve the solids. The solution was cooled (0 °C) and then combined with boron tribromide (400 μL of 1 M in dichloromethane). The mixture was vortexed for 5 minutes, chilled for 30 minutes, and then vortexed at ambient temperature for 64 hours. Additional dichloromethane (500 μL) and boron tribromide (400 μL of 1 M in dichloromethane) were added and the mixture was vortexed overnight. The solvent was then removed by vacuum centrifugation. The residue was diluted with methanol (500 μL) and hydrochloric acid (500 μL of 6 N). The solvents were removed by vacuum centrifugation. The compounds were purified according to the method described in Examples 8 – 72. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



Example	Reagent	R	Measured Mass (M+H)
151	None	—H	286.1658
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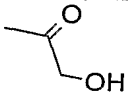
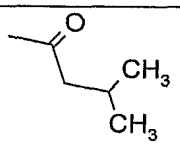
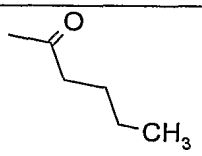
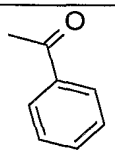
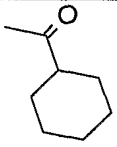
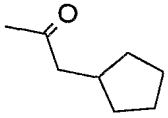
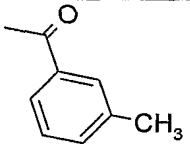
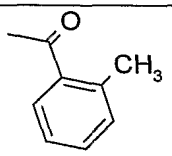
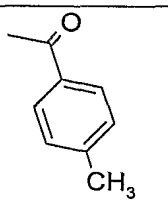
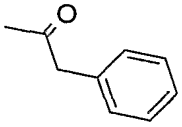
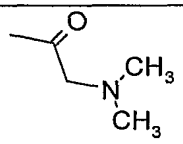
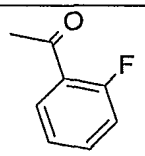
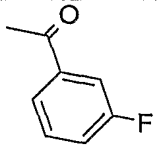
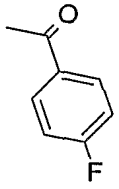
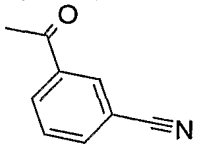
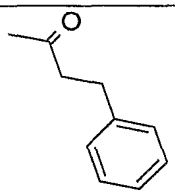
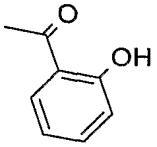
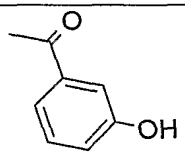
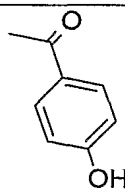
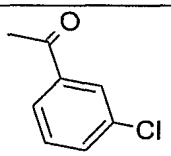
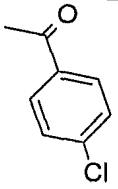
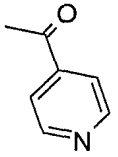
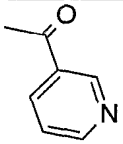
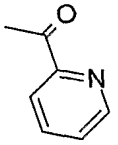
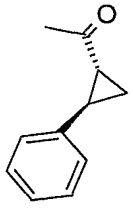
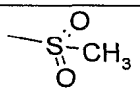
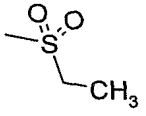
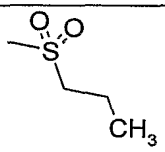
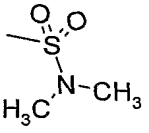
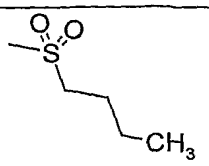
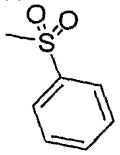
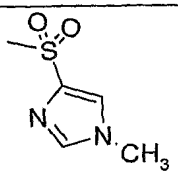
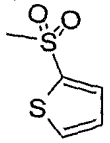
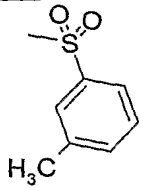
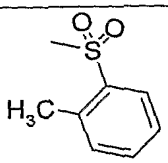
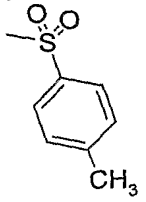
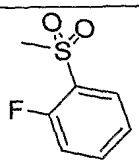
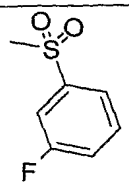
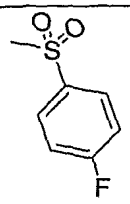
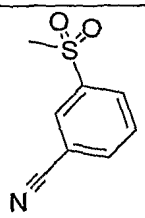
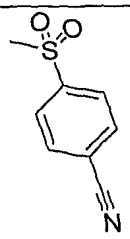
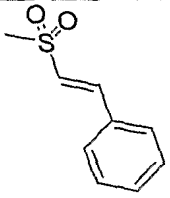
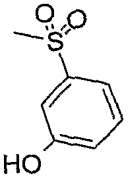
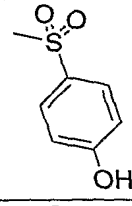
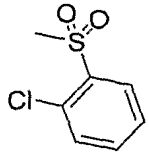
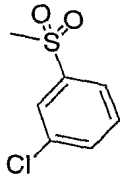
153	Methoxyacetyl chloride		344.1699

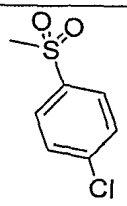
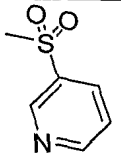
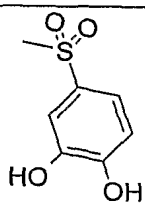
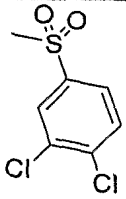
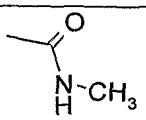
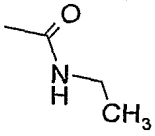
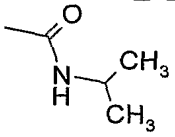
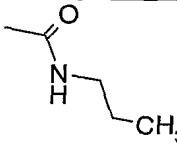
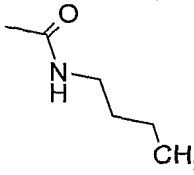
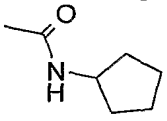
154	Cyclobutanecarbonyl chloride		368.2050
155	Isovaleryl chloride		370.2206
156	Pentanoyl chloride		370.2208
157	Benzoyl chloride		390.1909
158	Cyclohexanecarbonyl chloride		396.2412
159	Cyclopentylacetyl chloride		396.2411
160	*m*-Toluoyl chloride		404.2069
161	*o*- Toluoyl chloride		404.2072
162	*p*- Toluoyl chloride		404.2108
163	Phenylacetyl chloride		404.2056

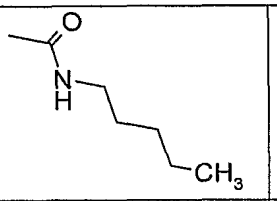
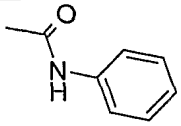
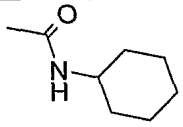
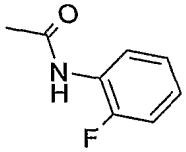
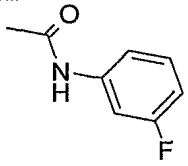
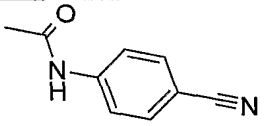
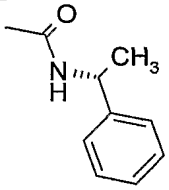
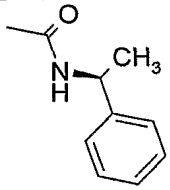
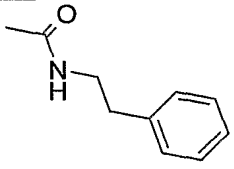
164	Dimethylaminoacetyl chloride hydrochloride		371.2157
165	2-Fluorobenzoyl chloride		408.1819
166	3-Fluorobenzoyl chloride		408.1811
167	4-Fluorobenzoyl chloride		408.1819
168	3-Cyanobenzoyl chloride		415.1847
169	Hydrocinnamoyl chloride		418.2200
170	2-Methoxybenzoyl chloride		406.1880
171	3-Methoxybenzoyl chloride		406.1876
172	*p*-Anisoyl chloride		406.1860

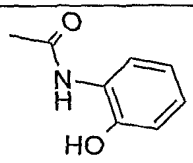
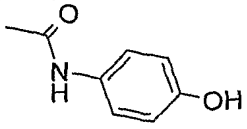
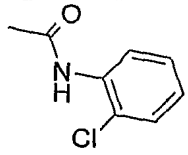
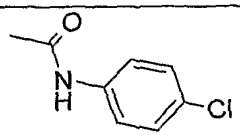
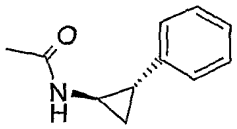
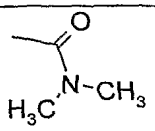
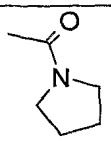
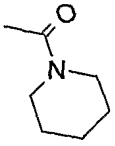
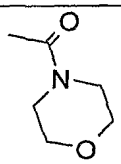
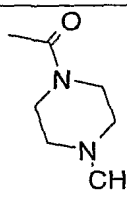
173	3-Chlorobenzoyl chloride		424.1517
174	4-Chlorobenzoyl chloride		424.1525
175	Isonicotinoyl chloride hydrochloride		391.1874
176	Nicotinoyl chloride hydrochloride		391.1895
177	Picolinoyl chloride hydrochloride		391.1846
178	*trans*-2-Phenyl-1-cyclopropanecarbonyl chloride		430.2213
179	Methanesulfonyl chloride		364.1421
180	Ethanesulfonyl chloride		378.1595
181	1-Propanesulfonyl chloride		392.1753
182	Dimethylsulfamoyl chloride		393.1685

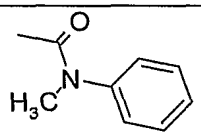
183	1-Butanesulfonyl chloride		406.1881
184	Benzenesulfonyl chloride		426.1591
185	1-Methylimidazole-4-sulfonyl chloride		430.1668
186	2-Thiophenesulfonyl chloride		432.1135
187	3-Methylbenzenesulfonyl chloride		440.1728
188	*o*-Toluenesulfonyl chloride		440.1758
189	*p*-Toluenesulfonyl chloride		440.1766
190	2-Fluorobenzenesulfonyl chloride		444.1479
191	3-Fluorobenzenesulfonyl chloride		444.1517

192	4-Fluorobenzenesulfonyl chloride		444.1496
193	3-Cyanobenzenesulfonyl chloride		451.1568
194	4-Cyanobenzenesulfonyl chloride		451.1579
195	*beta*-Styrenesulfonyl chloride		452.1725
196	3-Methoxybenzenesulfonyl chloride		442.1534
197	4-Methoxybenzenesulfonyl chloride		442.1557
198	2-Chlorobenzenesulfonyl chloride		460.1173
199	3-Chlorobenzenesulfonyl chloride		460.1242

200	4-Chlorobenzenesulfonyl chloride		460.1191
201	3-Pyridinesulfonyl chloride hydrochloride		427.1530
202	3,4-Dimethoxybenzenesulfonyl chloride		458.1452
203	3,4-Dichlorobenzenesulfonyl chloride		494.0806
204	Methyl isocyanate		343.1862
205	Ethyl isocyanate		357.2018
206	Isopropyl isocyanate		371.2181
207	*n*-Propyl isocyanate		371.2187
208	*n*-Butyl isocyanate		385.2314
209	Cyclopentyl isocyanate		397.2312

210	Pentyl isocyanate		399.2512
211	Phenyl isocyanate		405.2047
212	Cyclohexyl isocyanate		411.2473
213	2-Fluorophenyl isocyanate		423.1959
214	3-Fluorophenyl isocyanate		423.1924
215	4-Cyanophenyl isocyanate		430.1979
216	(*R*)-(+)-*alpha*-Methylbenzyl isocyanate		433.2370
217	(*S*)-(-)- *alpha*-Methylbenzyl isocyanate		433.2327
218	2-Phenylethylisocyanate		433.2333

219	2-Methoxyphenyl isocyanate		421.2006
220	4-Methoxyphenyl isocyanate		421.1958
221	2-Chlorophenyl isocyanate		439.1650
222	4-Chlorophenyl isocyanate		439.1656
223	*trans*-2-Phenylcyclopropyl isocyanate		445.2328
224	*N*,*N*-Dimethylcarbamoyl chloride		357.2005
225	1-Pyrrolidinecarbonyl chloride		383.2168
226	1-Piperidinecarbonyl chloride		397.2329
227	4-Morpholinylcarbonyl chloride		399.2112
228	4-Methyl-1-Piperazinecarbonyl chloride		412.2439

229	*N*-Methyl-*N*-phenylcarbamoyl chloride		419.2167

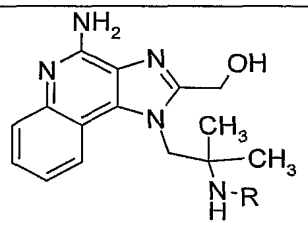
Examples 230 – 245

Part A

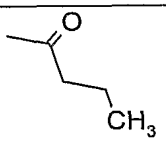
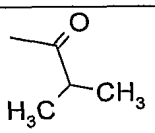
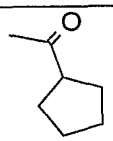
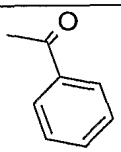
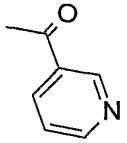
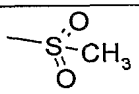
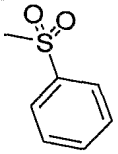
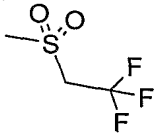
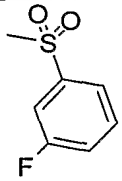
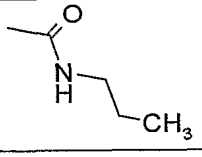
A solution of 1-(2-amino-2-methylpropyl)-2-methoxymethyl-1*H*-imidazo[4,5-*c*]quinoline-4-amine (31 mg, 1 eq, prepared according to the general method of Example 3 using methoxyacetyl chloride in lieu of 3-methoxypropionyl chloride and *tert*-butyl *N*-{2-[(3-aminoquinolin-4-yl)amino]-1,1-dimethylethyl}carbamate in lieu of *tert*-butyl *N*-{4-[(3-aminoquinolin-4-yl)amino]butyl}carbamate) and *N,N*-diisopropylethylamine (2 eq) in *N,N*-dimethylacetamide (1 mL) was placed in a test tube. A reagent (1.1 eq) from the table below was added and the reaction mixture was vortexed overnight. The reaction was quenched with concentrated ammonium hydroxide (100 µL) and the solvents were removed by vacuum centrifugation.

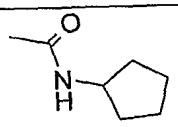
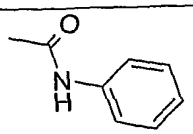
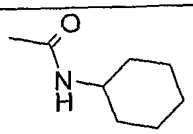
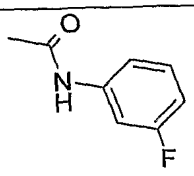
Part B

The residue (in a test tube) was combined with dichloromethane (1 mL) and the tube was vortexed to dissolve the solids. The solution was cooled (0 °C) and then combined with boron tribromide (400 µL of 1 M in dichloromethane). The reaction was maintained at about 0 °C for 20 minutes. Methanol (1 mL) and hydrochloric acid (500 µL of 6 N) were added and the tube was vortexed for about 30 minutes. The solvents were removed by vacuum centrifugation. The compounds were purified according to the method described in Examples 8 – 72. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



Example	Reagent	R	Measured Mass (M+H)

230	None		286.1687
231	Cyclopropanecarbonyl chloride		354.1936
232	Butyryl chloride		356.2094
233	Isobutyryl chloride		356.2119
234	Cyclopentanecarbonyl chloride		382.2259
235	Benzoyl chloride		390.1908
236	Nicotinoyl chloride hydrochloride		391.1844
237	Methanesulfonyl chloride		364.1414
238	Benzenesulfonyl chloride		426.1617
239	2,2,2-Trifluoroethanesulfonyl chloride		432.1339
240	3-Fluorobenzenesulfonyl chloride		444.1523
241	*n*-Propyl isocyanate		371.2215

242	Cyclopentyl isocyanate		397.2327
243	Phenyl isocyanate		405.2063
244	Cyclohexyl isocyanate		411.2515
245	3-Fluorophenyl isocyanate		423.1955

Examples 246 – 257

Part A

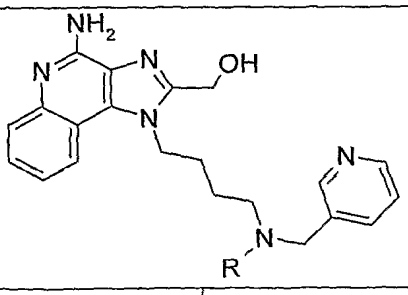
To a round-bottomed flask containing 1-(4-aminobutyl)-2-methoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (10.0 g, 33.4 mmol) was added methanol (160 mL) followed by acetic acid (40 mL). The reaction was stirred for 5 minutes and pyridine 3-carboxaldehyde (5.4 g, 50.1 mmol) was added and the reaction was stirred overnight at ambient temperature. Sodium cyanoborohydride (1 M in THF, 33.4 mL, 33.4 mmol) was added to the resultant imine in portions over 10 minutes. After 45 minutes the solvent was evaporated to afford an oil. To the oil was added saturated aqueous sodium bicarbonate (200 mL) and the aqueous layer was washed with ethyl acetate (200 mL) and dichloromethane (200 mL). The product was extracted from the aqueous with 20% methanol (2 x 100 mL) in dichloromethane. The organic layers were combined and the solvent evaporated to afford crude 2-methoxymethyl-1-{4-[(pyridin-3-ylmethyl)amino]butyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine (about 2 g). The aqueous layer was again extracted with 20% dimethylformamide (2 x 100 mL) in dichloromethane. The organic layers were combined and the solvent evaporated to afford crude 2-methoxymethyl-1-{4-[(pyridin-3-ylmethyl)amino]butyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine (about 2 g).

Part B

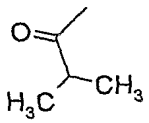
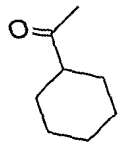
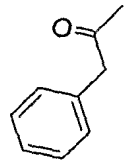
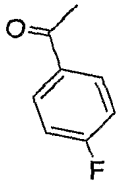
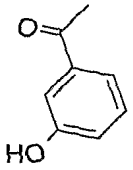
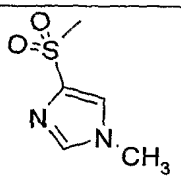
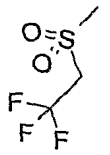
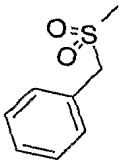
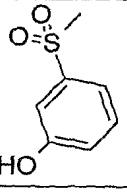
A solution of 2-methoxymethyl-1-{4-[(pyridin-3-ylmethyl)amino]butyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine (40 mg, 1 eq) and *N,N*-diisopropylethylamine (2 eq) in *N,N*-dimethylacetamide (1 mL) was added to a tube containing a reagent (1.1 eq) from the table below. The reaction mixture was vortexed for 4 hours and then quenched with water (50 μL). The solvents were removed by vacuum centrifugation. The residue was purified by solid-supported liquid-liquid extraction according to the following procedure. The sample was dissolved in chloroform (1 mL) then loaded onto diatomaceous earth that had been equilibrated with 1 M sodium hydroxide (600 μL) for about 20 minutes. After 10 minutes chloroform (500 μL) was added to elute the product from the diatomaceous earth into a well of a collection plate. After an additional 10 minutes the process was repeated with additional chloroform (500 μL). The solvent was then removed by vacuum centrifugation.

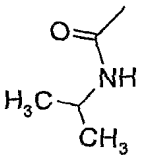
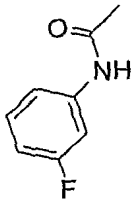
Part C

The residue (in a test tube) was combined with dichloromethane (500 μL) and the tube was vortexed to dissolve the solids. The solution was cooled (0 °C) and then combined with boron tribromide (400 μL of 1 M in dichloromethane). The mixture was vortexed for 10 minutes, chilled for 30 minutes, and then vortexed at ambient temperature overnight. The solvent was then removed by vacuum centrifugation. The residue was diluted with methanol (500 μL) and hydrochloric acid (500 μL of 6 N) and the mixture was vortexed for about 30 minutes. The solvents were removed by vacuum centrifugation. The compounds were purified according to the method described in Examples 8 – 72. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



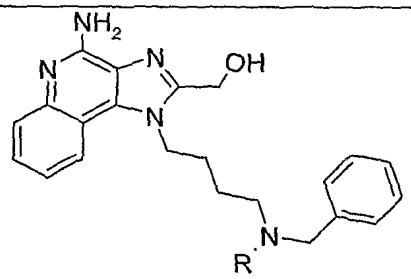
Example	Reagent	R	Measured Mass (M+H)

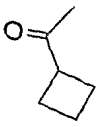
246	None		377.2087
247	Isobutyryl chloride		447.2468
248	Cyclohexanecarbonyl chloride		487.2783
249	Phenylacetyl chloride		495.2465
250	4-Fluorobenzoyl chloride		499.2272
251	3-Methoxybenzoyl chloride		497.2263
252	1-Methylimidazole-4-sulfonyl chloride		521.2071
253	2,2,2-Trifluoroethanesulfonyl chloride		523.1717
254	*alpha*-Toluenesulfonyl chloride		531.2134
255	3-Methoxybenzenesulfonyl chloride		533.1941

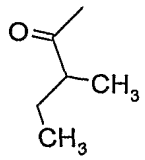
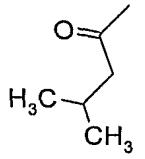
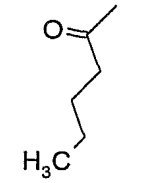
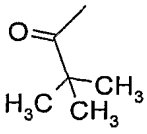
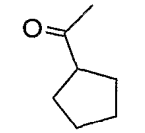
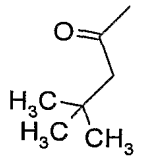
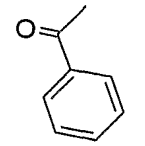
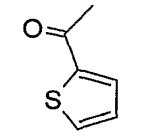
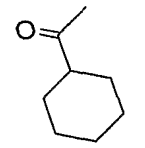
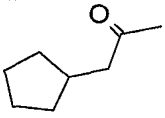
256	Isopropyl isocyanate		462.2611
257	3-Fluorophenyl isocyanate		514.2357

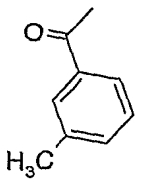
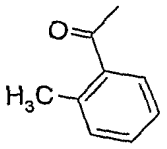
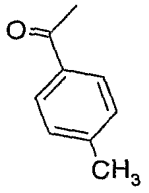
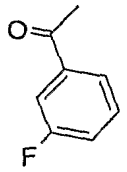
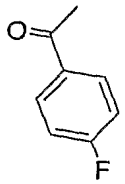
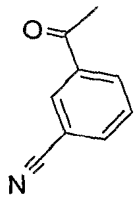
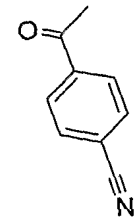
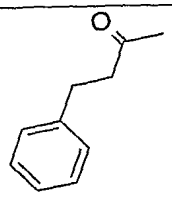
Examples 258 – 322

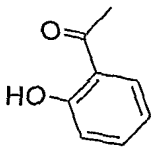
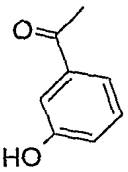
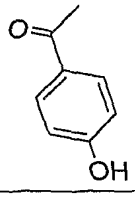
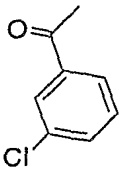
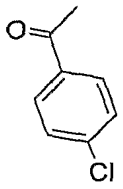
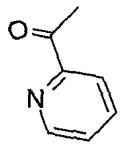
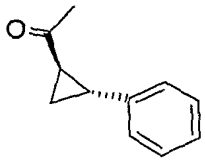
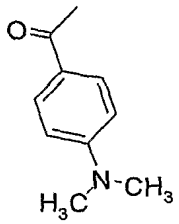
The compounds in the table below were prepared and purified according to the methods of Parts B and C of Examples 246 – 257 using 1-(4-benzylaminobutyl)-2-ethoxymethy-1*H*-imidazo[4,5-*c*]quinolin-4-amine in lieu of 2-methoxymethyl-1-{4-[(pyridin-3-ylmethyl)amino]butyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine. 1-(4-Benzylaminobutyl)-2-ethoxymethy-1*H*-imidazo[4,5-*c*]quinolin-4-amine was prepared according to the general method of Part A of Examples 246 – 257 using benzaldehyde in lieu of pyridine 3-carboxaldehyde and 1-(4-aminobutyl)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine in lieu of 1-(4-aminobutyl)-2-methoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

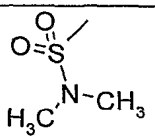
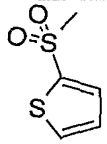
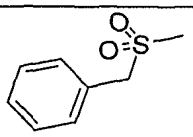
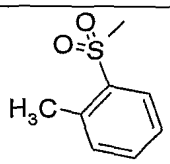
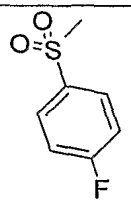
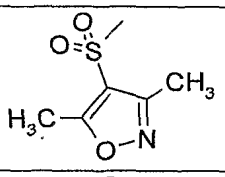
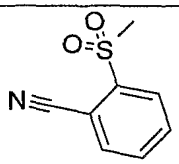
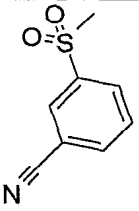


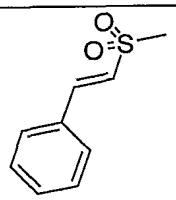
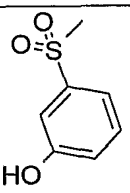
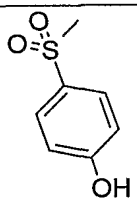
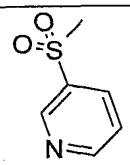
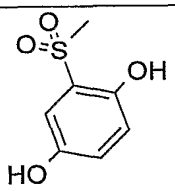
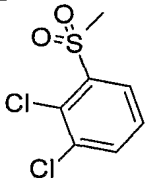
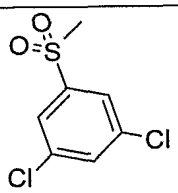
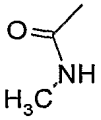
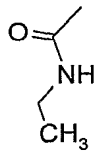
Example	Reagent	R	Measured Mass (M+H)
258	Cyclobutanecarbonyl chloride		458.2550

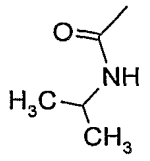
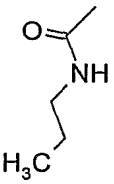
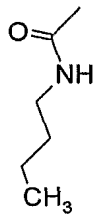
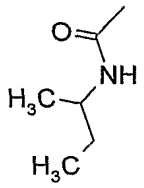
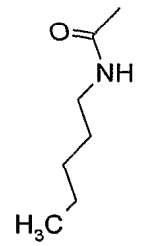
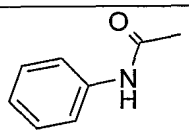
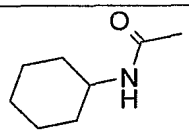
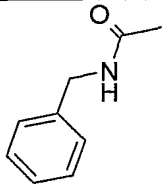
259	*DL*-2-Methylbutyryl chloride		460.2707
260	Isovaleryl chloride		460.2714
261	Pentanoyl chloride		460.2730
262	Pivaloyl chloride		460.2714
263	Cyclopentanecarbonyl chloride		472.2712
264	*tert*-Butylacetyl chloride		474.2879
265	Benzoyl chloride		480.2398
266	Thiophene-2-carbonyl chloride		486.1971
267	Cyclohexanecarbonyl chloride		486.2893
268	Cyclopentylacetyl chloride		486.2818

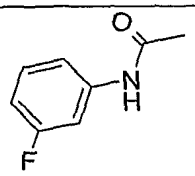
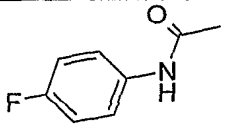
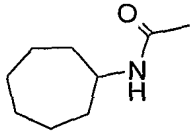
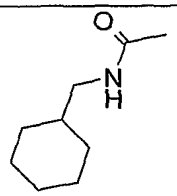
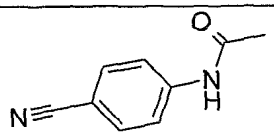
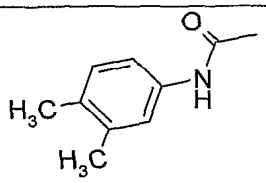
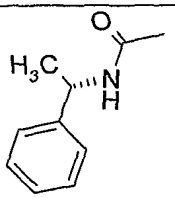
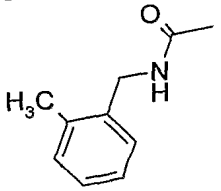
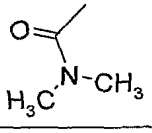
269	*m*-Toluoyl chloride		494.2577
270	*o*-Toluoyl chloride		494.2531
271	*p*-Toluoyl chloride		494.2527
272	3-Fluorobenzoyl chloride		498.2307
273	4-Fluorobenzoyl chloride		498.2326
274	3-Cyanobenzoyl chloride		505.2378
275	4-Cyanobenzoyl chloride		505.2387
276	Hydrocinnamoyl chloride		508.2715

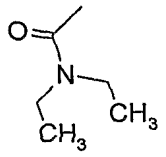
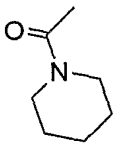
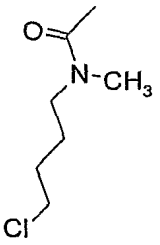
277	2-Methoxybenzoyl chloride		496.2311
278	3-Methoxybenzoyl chloride		496.2314
279	*p*-Anisoyl chloride		496.2365
280	3-Chlorobenzoyl chloride		514.2026
281	4-Chlorobenzoyl chloride		514.2041
282	Picolinoyl chloride hydrochloride		481.2361
283	*trans*-2-Phenyl-1-cyclopropanecarbonyl chloride		520.2695
284	4-Dimethylaminobenzoyl chloride		523.2802

285	1-Propanesulfonyl chloride		482.2232
286	Dimethylsulfamoyl chloride		483.2196
287	2-Thiophenesulfonyl chloride		522.1613
288	*alpha*-Toluenesulfonyl chloride		530.2239
289	*o*-Toluenesulfonyl chloride		530.2197
290	4-Fluorobenzenesulfonyl chloride		534.2028
291	3,5-Dimethylisoxazole-4-sulfonyl chloride		535.2106
292	2-Cyanobenzenesulfonyl chloride		541.1968
293	3-Cyanobenzenesulfonyl chloride		541.2035

294	*beta*-Styrene sulfonyl chloride		542.2234
295	3-Methoxybenzenesulfonyl chloride		532.2052
296	4-Methoxybenzenesulfonyl chloride		532.2037
297	3-Pyridine sulfonyl chloride hydrochloride		517.2015
298	2,5-Dimethoxybenzenesulfonyl chloride		548.1964
299	2,3-Dichlorobenzenesulfonyl chloride		584.1294
300	3,5-Dichlorobenzenesulfonyl chloride		584.1282
301	Methyl isocyanate		433.2361
302	Ethyl isocyanate		447.2538

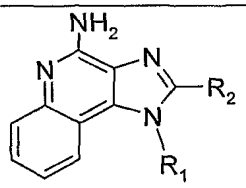
303	Isopropyl isocyanate		461.2663
304	*n*-Propyl isocyanate		461.2691
305	*n*-Butyl isocyanate		475.2860
306	*sec*-Butyl isocyanate		475.2849
307	Pentyl isocyanate		489.3005
308	Phenyl isocyanate		495.2511
309	Cyclohexyl isocyanate		501.2978
310	Benzyl isocyanate		509.2675

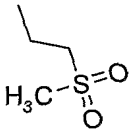
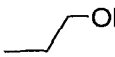
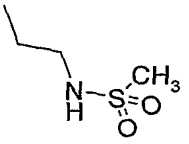
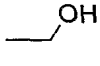
311	3-Fluorophenyl isocyanate		513.2467
312	4-Fluorophenyl isocyanate		513.2388
313	Cycloheptyl isocyanate		515.3081
314	Cyclohexanemethyl isocyanate		515.3163
315	4-Cyanophenyl isocyanate		520.2483
316	3,4-Dimethylphenyl isocyanate		523.2786
317	(*S*)-(-)-*alpha*-Methylbenzyl isocyanate		523.2786
318	2-Methylbenzyl isocyanate		523.2860
319	*N*,*N*-Dimethylcarbamoyl chloride		447.2511

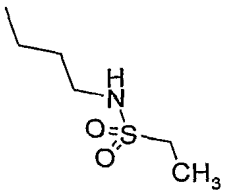
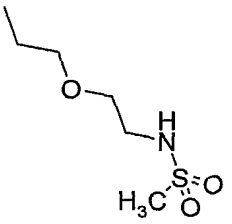
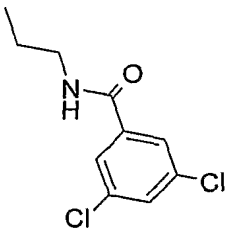
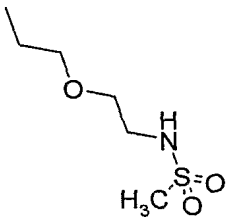
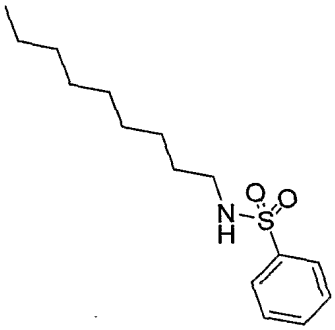
320	Diethylcarbamyl chloride		475.2828
321	1-Piperidinecarbonyl chloride		487.2839
322	*N*-(4-Chlorobutyl)-*N*-methylcarbamyl chloride		523.2588

Examples 323 – 329

The compounds in the table below were prepared according to the general method of Examples 111 – 140. The table shows a reference for the ether starting material, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



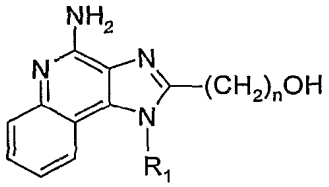
Example	Reference (ether)	R_1	R_2	Measured Mass (M+H)
323	U.S. Patent No. 6,667,312*			335.1158
324	U.S. Patent No. 6,677,349*			336.1098

325	U.S. Patent No. 6,677,349*			364.1454
326	U.S. Patent No. 6,677,347 Example 57			380.1391
327	U.S. Patent No. 6,756,382*			444.0999
328	U.S. Patent No. *6,683,088* Example 1			394.1588
329	U.S. Patent No. 6,677,349 Example 242			496.2401

*Although not specifically exemplified, the compound is readily prepared using the disclosed synthetic methods.

Exemplary Compounds

Certain exemplary compounds, including some of those described above in the Examples, have the following Formula Ib and the following substituents n and R_1 wherein each line of the table is matched to Formula Ib to represent a specific embodiment of the invention.



Ib

n	R_1
1	2-[(cyclohexylcarbonyl)amino]-2-methylpropyl
1	2-[(cyclopropylcarbonyl)amino]ethyl
1	4-[(cyclopropylcarbonyl)amino]butyl
1	2-{[(1-methylethyl)carbonyl]amino}ethyl
1	4-{[(1-methylethyl)carbonyl]amino}butyl
1	2,2-dimethyl-3-(methylsulfonyl)propyl
1	2-methyl-2-({[(1-methylethyl)amino]carbonyl}amino)propyl
1	2-methyl-2-[(methylsulfonyl)amino]propyl
1	4-[(methylsulfonyl)amino]butyl
1	2-[(methylsulfonyl)amino]ethyl
1	4-[(4-morpholinecarbonyl)amino]butyl
1	2-[(4-morpholinecarbonyl)amino]ethyl
1	tetrahydro-2*H*-pyran-4-ylmethyl
2	2-[(cyclohexylcarbonyl)amino]-2-methylpropyl
2	2-[(cyclopropylcarbonyl)amino]ethyl
2	4-[(cyclopropylcarbonyl)amino]butyl
2	2-{[(1-methylethyl)carbonyl]amino}ethyl
2	4-{[(1-methylethyl)carbonyl]amino}butyl
2	2,2-dimethyl-3-(methylsulfonyl)propyl
2	2-methyl-2-({[(1-methylethyl)amino]carbonyl}amino)propyl
2	2-methyl-2-[(methylsulfonyl)amino]propyl
2	4-[(methylsulfonyl)amino]butyl
2	2-[(methylsulfonyl)amino]ethyl
2	4-[(4-morpholinecarbonyl)amino]butyl

2	2-[(4-morpholinecarbonyl)amino]ethyl
2	tetrahydro-2*H*-pyran-4-ylmethyl

CYTOKINE INDUCTION IN HUMAN CELLS

An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon (α) and tumor necrosis factor (α) (IFN-α and TNF-α, respectively) secreted into culture media as described by Testerman et. al. in "Cytokine Induction by the Immunomodulators Imiquimod and S-27609", *Journal of Leukocyte Biology*, *58*, 365-372 (September, 1995).

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into vacutainer tubes or syringes containing EDTA. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077 (Sigma, St. Louis, MO) or Ficoll-Paque Plus (Amersham Biosciences Piscataway, NJ). Blood is diluted 1:1 with Dulbecco's Phosphate Buffered Saline (DPBS) or Hank's Balanced Salts Solution (HBSS). Alternately, whole blood is placed in Accuspin (Sigma) or LeucoSep (Greiner Bio-One, Inc., Longwood, FL) centrifuge frit tubes containing density gradient medium. The PBMC layer is collected and washed twice with DPBS or HBSS and re-suspended at 4 x 10^6 cells/mL in RPMI complete. The PBMC suspension is added to 96 well flat bottom sterile tissue culture plates containing an equal volume of RPMI complete media containing test compound.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. The compounds are generally tested at concentrations ranging from 30-0.014 μM. Controls include cell samples with media only, cell samples with DMSO only (no compound), and cell samples with reference compound.

Incubation

The solution of test compound is added at 60 μM to the first well containing RPMI complete and serial 3 fold dilutions are made in the wells. The PBMC suspension is then added to the wells in an equal volume, bringing the test compound concentrations to the desired range (usually 30-0.014 μM). The final concentration of PBMC suspension is 2 x 10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 x g) at 4°C. The cell-free culture supernatant is removed and transferred to sterile polypropylene tubes. Samples are maintained at -30 to -70°C until analysis. The samples are analyzed for IFN-α by ELISA and for TNF-α by IGEN/BioVeris Assay.

Interferon (α) and Tumor Necrosis Factor (α) Analysis

IFN-α concentration is determined with a human multi-subtype colorimetric sandwich ELISA (Catalog Number 41105) from PBL Biomedical Laboratories, Piscataway, NJ. Results are expressed in pg/mL.

The TNF-α concentration is determined by ORIGEN M-Series Immunoassay and read on an IGEN M-8 analyzer from BioVeris Corporation, formerly known as IGEN International, Gaithersburg, MD. The immunoassay uses a human TNF-α capture and detection antibody pair (Catalog Numbers AHC3419 and AHC3712) from Biosource International, Camarillo, CA. Results are expressed in pg/mL.

Assay Data and Analysis

In total, the data output of the assay consists of concentration values of TNF-α and IFN-α (y-axis) as a function of compound concentration (x-axis).

Analysis of the data has two steps. First, the greater of the mean DMSO (DMSO control wells) or the experimental background (usually 20 pg/mL for IFN-α and 40 pg/mL for TNF-α) is subtracted from each reading. If any negative values result from background subtraction, the reading is reported as " * ", and is noted as not reliably

detectable. In subsequent calculations and statistics, " * ", is treated as a zero. Second, all background subtracted values are multiplied by a single adjustment ratio to decrease experiment to experiment variability. The adjustment ratio is the area of the reference compound in the new experiment divided by the expected area of the reference compound based on the past 61 experiments (unadjusted readings). This results in the scaling of the reading (y-axis) for the new data without changing the shape of the dose-response curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91) and the expected area is the sum of the median dose values from the past 61 experiments.

The minimum effective concentration is calculated based on the background-subtracted, reference-adjusted results for a given experiment and compound. The minimum effective concentration (μmolar) is the lowest of the tested compound concentrations that induces a response over a fixed cytokine concentration for the tested cytokine (usually 20 pg/mL for IFN-α and 40 pg/mL for TNF-α). The maximal response (pg/mL) is the maximal response attained in the dose response curve.

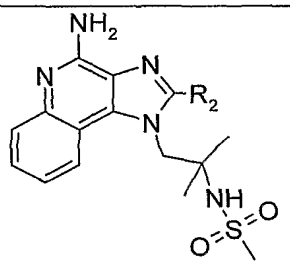
Compounds of the invention and close analogs were tested for their ability to induce cytokine biosynthesis using the test method described above. The analogs used are shown in the table below.

Analog	Chemical Name	Reference
1	*N*-[2-(4-Amino-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]methanesulfonamide	U.S. Patent 6,677,349[#]
2	*N*-[2-(4-Amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]methanesulfonamide	U.S. Patent 6,677,349[#]
3	*N*-[2-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]methanesulfonamide	U.S. Patent 6,677,349[#]
4	*N*-[2-(4-Amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]methanesulfonamide	U.S. Patent 6,677,349 Example 268
5	*N*-{2-[4-Amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1,1-dimethylethyl}methanesulfonamide	Example 6 Part D

[#]This compound is not specifically exemplified but can be readily prepare using the synthetic methods disclosed in the cited reference

The compounds of Examples 6 and 7 and several closely related analogs were tested using the test method described above. The IFN-α dose response curves for Example 6, Analog 2, Analog 3 and Analog 5 are shown in Figure 1. The TNF-α dose response curves for Example 6, Analog 2, Analog 3 and Analog 5 are shown in Figure 2. The IFN-α dose response curves for Example 7, Analog 1, Analog 2 and Analog 4 are shown in Figure 3. The TNF-α dose response curves for Example 7, Analog 1, Analog 2 and Analog 4 are shown in Figure 4. The minimum effective concentration for the induction of IFN-α, minimum effective concentration for the induction of TNF-α, the maximal response for IFN-α, and the maximal response for TNF-α are shown in Table 5 below where # is the number of separate experiments in which the compound was tested. When a compound was tested in more than one experiment the values shown are the median values.

Table 5



Compound	R_2	Minimum Effective Concentration (μM)		Maximal Response (pg/mL)		#
		IFN	TNF	IFN	TNF	
Example 7	$-CH_2OH$	3.330	30.00	2250	121	5
Example 6	$-(CH_2)_2OH$	1.11	>30	7521	*	3
Analog 1	$-CH_3$	0.370	3.330	1846	1518	7
Analog 2	$-CH_2CH_3$	0.120	1.110	831	3670	4
Analog 3	$-(CH_2)_2CH_3$	0.120	0.370	832	7245	9
Analog 4	$-CH_2OCH_2CH_3$	0.040	0.370	889	10125	22
Analog 5	$-(CH_2)_2OCH_3$	0.014	0.12	825	12518	6

*TNF below experimental background of 40 pg/mL.

Compounds of the invention and close analogs were tested for their ability to induce cytokine biosynthesis using the test method described above. The minimum

effective concentration for the induction of IFN-α, minimum effective concentration for the induction of TNF-α, the maximal response for IFN-α, and the maximal response for TNF-α are shown in Table 6 below where # is the number of separate experiments in which the compound was tested. When a compound was tested in more than one experiment the values shown are the median values.

Table 6

Compound	R_1	R_2	Minimum Effective Concentration (μM)		Maximal Response (pg/mL)		#
			IFN	TNF	IFN	TNF	
Example 7	$-CH_2C(CH_3)_2NHS(O)_2CH_3$	$-CH_2OH$	3.33	30	1670	154	6
Example 6	$-CH_2C(CH_3)_2NHS(O)_2CH_3$	$-(CH_2)_2OH$	1.11	30	6527	*	4
Analog 1	$-CH_2C(CH_3)_2NHS(O)_2CH_3$	$-CH_3$	0.37	3.33	1846	1518	9
Analog 2	$-CH_2C(CH_3)_2NHS(O)_2CH_3$	$-CH_2CH_3$	0.12	1.11	1096	9675	6
Analog 3	$-CH_2C(CH_3)_2NHS(O)_2CH_3$	$-CH_2CH_2CH_3$	0.12	0.37	832	9780	11
Analog 4	$-CH_2C(CH_3)_2NHS(O)_2CH_3$	$-CH_2OCH_2CH_3$	0.04	0.37	1138	10665	33
Analog 5	$-CH_2C(CH_3)_2NHS(O)_2CH_3$	$-(CH_2)_2OCH_3$	0.014	0.12	1308	13908	8
Analog 6	$-CH_2C(CH_3)_2NHS(O)_2CH_3$	$-CH_2OCH_3$	0.37	3.33	1638	7151	1
Example 147	$-(CH_2)_4NHS(O)_2CH_3$	$-CH_2OH$	0.37	>30	7220	*	3
Example 3	$-(CH_2)_4NHS(O)_2CH_3$	$-(CH_2)_2OH$	0.37	>30	2340	*	4
Analog 7	$-(CH_2)_4NHS(O)_2CH_3$	$-CH_3$	0.12	10	7293	526	13
Analog 8	$-(CH_2)_4NHS(O)_2CH_3$	$-CH_2CH_3$	0.04	3.33	2712	679	79
Analog 9	$-(CH_2)_4NHS(O)_2CH_3$	$-CH_2CH_2CH_3$	0.12	1.11	2184	850	22
Analog 10	$-(CH_2)_4NHS(O)_2CH_3$	$-CH_2OCH_2CH_3$	0.04	1.11	2581	1439	10

Analog 11	$-(CH_2)_4NHS(O)_2CH_3$	$-(CH_2)_2OCH_3$	0.014	0.37	7594	1931	13
Example 115	$-(CH_2)_4NHC(O)-N$	$-(CH_2)_2OH$	1.11	>30	8361	*	1
Analog 12	$-(CH_2)_4NHC(O)-N$	$-CH_3$	0.12	10	1538	1400	1
Analog 13	$-(CH_2)_4NHC(O)-N$	$-CH_2CH_3$	0.37	3.33	4975	2570	1
Analog 14	$-(CH_2)_4NHC(O)-N$	$-CH_2CH_2CH_3$	0.12	1.11	11255	1298	3
Analog 15	$-(CH_2)_4NHC(O)-N$	$-CH_2OCH_2CH_3$	0.12	1.11	3433	1580	2
Analog 16	$-(CH_2)_4NHC(O)-N$	$-(CH_2)_2OCH_3$	0.014	0.04	8889	3494	8
Example 122	$-(CH_2)_3NHS(O)_2CH_3$	$-(CH_2)_2OH$	3.33	>30	9651	*	3
Analog 17	$-(CH_2)_3NHS(O)_2CH_3$	$-CH_3$	1.11	30	2778	*	11
Analog 18	$-(CH_2)_3NHS(O)_2CH_3$	$-CH_2CH_3$	1.11	30	1912	238	2
Analog 19	$-(CH_2)_3NHS(O)_2CH_3$	$-CH_2CH_2CH_3$	1.11	10	2148	109	3
Analog 20	$-(CH_2)_3NHS(O)_2CH_3$	$-CH_2OCH_2CH_3$	0.37	10	1338	463	9
Analog 21	$-(CH_2)_3NHS(O)_2CH_3$	$-(CH_2)_2OCH_3$	0.014	1.11	3995	954	9
Example 131	$-CH_2C(CH_3)_2CH_2NHS(O)_2CH_3$	$-(CH_2)_2OH$	0.37	>30	8361	*	1
Analog 22	$-CH_2C(CH_3)_2CH_2NHS(O)_2CH_3$	$-CH_3$	0.37	10	1019	805	2
Analog 23	$-CH_2C(CH_3)_2CH_2NHS(O)_2CH_3$	$-CH_2CH_3$	0.12	3.33	1431	1453	3

Analog 24	$-CH_2C(CH_3)_2CH_2NHS(O)_2CH_3$	$-CH_2CH_2CH_3$	0.12	10	1929	2
Analog 25	$-CH_2C(CH_3)_2CH_2NHS(O)_2CH_3$	$-CH_2OCH_2CH_3$	0.12	0.37	3768	5
Analog 26	$-CH_2C(CH_3)_2CH_2NHS(O)_2CH_3$	$-(CH_2)_2OCH_3$	0.014	0.04	5467	10
Example 36	$-(CH_2)_2NHS(O)_2CH_3$	$-(CH_2)_2OH$	10	>30	*	1
Analog 27	$-(CH_2)_2NHS(O)_2CH_3$	$-CH_3$	0.12	10	820	3
Analog 28	$-(CH_2)_2NHS(O)_2CH_3$	$-CH_2CH_3$	0.12	10	2401	6
Analog 29	$-(CH_2)_2NHS(O)_2CH_3$	$-CH_2CH_2CH_3$	30	10	11432	2
Analog 30	$-(CH_2)_2NHS(O)_2CH_3$	$-CH_2OCH_2CH_3$	0.12	3.33	4918	9
Analog 31	$-(CH_2)_2NHS(O)_2CH_3$	$-(CH_2)_2OCH_3$	0.014	0.04	8547	6
Example 125	$-(CH_2)_5S(O)_2CH_3$	$-(CH_2)_2OH$	0.37	>30	*	1
Analog 32	$-(CH_2)_5S(O)_2CH_3$	$-CH_3$	0.37	3.33	771	21
Analog 33	$-(CH_2)_5S(O)_2CH_3$	$-CH_2CH_3$	0.12	1.11	1545	7
Analog 34	$-(CH_2)_5S(O)_2CH_3$	$-CH_2CH_2CH_3$	0.12	1.11	848	3
Analog 35	$-(CH_2)_5S(O)_2CH_3$	$-(CH_2)_2OCH_3$	0.014	1.11	6169	2
Example 133	$-(CH_2)_2O(CH_2)_2N(CH_3)S(O)_2CH_3$	$-(CH_2)_2OH$	0.37	>30	*	1
Analog 36	$-(CH_2)_2O(CH_2)_2N(CH_3)S(O)_2CH_3$	$-CH_3$	0.12	1.11	3571	1
Analog 37	$-(CH_2)_2O(CH_2)_2N(CH_3)S(O)_2CH_3$	$-CH_2CH_3$	0.12	1.11	2525	1
Analog 38	$-(CH_2)_2O(CH_2)_2N(CH_3)S(O)_2CH_3$	$-CH_2CH_2CH_3$	0.37	3.33	1312	2
Analog 39	$-(CH_2)_2O(CH_2)_2N(CH_3)S(O)_2CH_3$	$-(CH_2)_2OCH_3$	0.014	0.37	2191	4
Example 99	$-(CH_2)_3NHC(O)NHCH(CH_3)_2$	$-(CH_2)_2OH$	0.37	>30	*	1
Analog 40	$-(CH_2)_3NHC(O)NHCH(CH_3)_2$	$-CH_3$	3.33	10	490	1

Analog 41	-$(CH_2)_3NHC(O)NHCH(CH_3)_2$	-$CH_2CH_2CH_3$	0.12	1.11	6571	3740	2
Analog 42	-$(CH_2)_3NHC(O)NHCH(CH_3)_2$	-$(CH_2)_2OCH_3$	0.12	1.11	1289	1259	1
Example 120	-$(CH_2)_3NH_2$	-$(CH_2)_2OH$	3.33	>30	5636	*	1
Analog 43	-$(CH_2)_3NH_2$	-CH_3	3.33	>30	421	*	1
Analog 44	-$(CH_2)_3NH_2$	-$CH_2OCH_2CH_3$	0.12	30	1325	411	1
Analog 45	-$(CH_2)_3NH_2$	-$(CH_2)_2OCH_3$	0.04	1.11	3433	1674	1
Example 128	-$(CH_2)_3NHC(O)$-	-$(CH_2)_2OH$	30	>30	75	*	3
Analog 46	-$(CH_2)_3NHC(O)$-	-CH_3	0.37	30	4843	463	2
Analog 47	-$(CH_2)_3NHC(O)$-	-$CH_2OCH_2CH_3$	0.12	1.11	6670	1379	2
Analog 48	-$(CH_2)_3NHC(O)$-	-$(CH_2)_2OCH_3$	0.014	0.014	5915	6169	2
Example 130	-$CH_2C(CH_3)_2CH_2NHC(O)NH$-	-$(CH_2)_2OH$	0.014	3.33	8361	2001	1
Analog 49	-$CH_2C(CH_3)_2CH_2NHC(O)NH$-	-CH_2CH_3	0.014	0.12	922	2098	2
Analog 50	-$CH_2C(CH_3)_2CH_2NHC(O)NH$-	-$CH_2OCH_2CH_3$	0.014	0.04	1133	3618	2
Analog 51	-$CH_2C(CH_3)_2CH_2NHC(O)NH$-	-$(CH_2)_2OCH_3$	0.014	0.04	570	6449	2

Example 5		-CH_2OH	0.37	10	17274	1130	1
Analog 52		-$CH_2OCH_2CH_3$	0.37	0.37	1052	12173	13
Analog 53		-CH_2OCH_3	1.11	3.33	2518	9721	1
Example 124		-$(CH_2)_2OH$	0.12	3.33	3980	1446	1
Analog 54		-$CH_2OCH_2CH_3$	0.04	0.37	832	1820	5
Analog 55		-$(CH_2)_2OCH_3$	0.014	0.014	2133	1812	1
Example 126	-$(CH_2)_3NHC(O)NH(CH_2)_3CH_3$	-$(CH_2)_2OH$	1.11	>30	8361	*	1
Analog 56	-$(CH_2)_3NHC(O)NH(CH_2)_3CH_3$	-$CH_2OCH_2CH_3$	0.37	3.33	827	963	5
Analog 57	-$(CH_2)_3NHC(O)NH(CH_2)_3CH_3$	-$(CH_2)_2OCH_3$	0.014	0.04	5915	6169	2
Example 129	-$CH_2C(CH_3)_2CH_2NH_2$	-$(CH_2)_2OH$	0.37	30	2702	85	1
Analog 58	-$CH_2C(CH_3)_2CH_2NH_2$	-CH_2CH_3	0.04	0.37	405	13846	1
Analog 59	-$CH_2C(CH_3)_2CH_2NH_2$	-$(CH_2)_2OCH_3$	0.014	0.04	571	17626	1
Example 132	-$(CH_2)_3NHC(O)$-	-$(CH_2)_2OH$	0.37	>30	8361	*	1
Analog 60	-$(CH_2)_3NHC(O)$-	-CH_3	1.11	3.33	571	156	3

Analog 61	-$(CH_2)_3NHC(O)$-	-$(CH_2)_2OCH_3$	0.014	1.11	1504	3080	2
Example 137	-$(CH_2)_2NHC(O)NHCH_2CH_3$	-$(CH_2)_2OH$	30	30	801	73	1
Analog 62	-$(CH_2)_2NHC(O)NHCH_2CH_3$	-CH_2CH_3	3.33	10	1031	3250	2
Analog 63	-$(CH_2)_2NHC(O)NHCH_2CH_3$	-$(CH_2)_2OCH_3$	0.014	0.12	2587	7719	4
Example 138	-$(CH_2)_2NHC(O)CH_2CH(CH_3)_2$	-$(CH_2)_2OH$	3.33	>30	36	*	1
Analog 64	-$(CH_2)_2NHC(O)CH_2CH(CH_3)_2$	-CH_2CH_3	3.33	30	851	587	2
Analog 65	-$(CH_2)_2NHC(O)CH_2CH(CH_3)_2$	-$(CH_2)_2OCH_3$	0.12	3.33	1204	5694	5
Example 142	-$CH_2C(CH_3)_2NHC(O)NHCH(CH_3)_2$	-CH_2OH	1.11	>30	1554	*	1
Analog 66	-$CH_2C(CH_3)_2NHC(O)NHCH(CH_3)_2$	-$CH_2CH_2CH_3$	1.11	3.33	1428	6363	3
Analog 67	-$CH_2C(CH_3)_2NHC(O)NHCH(CH_3)_2$	-$CH_2OCH_2CH_3$	0.37	1.11	966	10587	4
Example 1	-$(CH_2)_3NHS(O)_2$-	-$(CH_2)_2OH$	0.37	10	1072	143	1
Analog 68	-$(CH_2)_3NHS(O)_2$-	-$(CH_2)_2OCH_3$	0.04	0.37	638	6169	2
Example 2	-$(CH_2)_3NHC(O)$-	-$(CH_2)_2OH$	3.33	3.33	507	45	1
Analog 69	-$(CH_2)_3NHC(O)$-	-$(CH_2)_2OCH_3$	0.12	1.11	647	6169	2
Example 4	-$CH_2C(CH_3)_2NH_2$	-CH_2OH	0.37	3.33	1893	41	2
Analog 70	-$CH_2C(CH_3)_2NH_2$	-$CH_2OCH_2CH_3$	0.12	0.37	656	11475	7

Example 111		-$(CH_2)_2$OH	0.12	1.11	7753	983	1
Analog 71		-$(CH_2)_2OCH_3$	0.014	0.04	2127	1462	7
Example 112		-$(CH_2)_2$OH	1.11	30	8361	76	1
Analog 72		-$(CH_2)_2OCH_3$	0.014	0.04	6032	3786	4
Example 114	-$(CH_2)_4NH_2$	-$(CH_2)_2$OH	30	>30	23	*	1
Analog 73	-$(CH_2)_4NH_2$	-$(CH_2)_2OCH_3$	0.04	0.37	127231	724	1
Example 116		-$(CH_2)_2$OH	0.37	30	8361	1112	1
Analog 74		-$(CH_2)_2OCH_3$	0.014	0.04	7545	9340	2
Example 117		-$(CH_2)_2$OH	0.37	3.33	5520	1938	1
Analog 75		-$(CH_2)_2OCH_3$	0.014	0.04	1129	7261	3

Example 118	-$(CH_2)_8$NHC(O)NH-	-$(CH_2)_2$OH	0.37	>30	5177	*	1
Analog 76	-$(CH_2)_8$NHC(O)NH-	-$(CH_2)_2OCH_3$	0.014	0.12	1257	1372	1
Example 119	-$(CH_2)_8$NHS(O)$_2CH_3$	-$(CH_2)_2$OH	0.04	3.33	8361	693	1
Analog 77	-$(CH_2)_8$NHS(O)$_2CH_3$	-$(CH_2)_2OCH_3$	0.014	0.014	1914	1853	2
Example 121	-$(CH_2)_8$NHC(O)-	-$(CH_2)_2$OH	0.37	3.33	2441	180	1
Analog 78	-$(CH_2)_8$NHC(O)-	-$(CH_2)_2OCH_3$	0.014	0.014	1584	1995	1
Example 134	-$(CH_2)_2O(CH_2)_2N(CH_3)C(O)$-	-$(CH_2)_2$OH	3.33	30	8361	315	1
Analog 79	-$(CH_2)_2O(CH_2)_2N(CH_3)C(O)$-	-$(CH_2)_2OCH_3$	0.04	0.37	1394	3317	1
Example 135	-$(CH_2)_2O(CH_2)_2N(CH_3)C(O)$-	-$(CH_2)_2$OH	3.33	30	2464	146	1
Analog 80	-$(CH_2)_2O(CH_2)_2N(CH_3)C(O)$-	-$(CH_2)_2OCH_3$	0.37	1.11	1234	4849	2
Example 140	-$(CH_2)_2O(CH_2)_2$NHC(O)$(CH_2)_{14}CH_3$	-$(CH_2)_2$OH	1.11	>30	673	*	1
Analog 81	-$(CH_2)_2O(CH_2)_2$NHC(O)$(CH_2)_{14}CH_3$	-$(CH_2)_2OCH_3$	0.014	0.014	2556	11033	9
Example 141	-$(CH_2)_3$NHC(O)CH$(CH_3)_2$	-$(CH_2)_2$OH	0.04	30	14046	243	1
Analog 82	-$(CH_2)_3$NHC(O)CH$(CH_3)_2$	-CH_3	1.11	10	3011	405	2
Example 143	-$CH_2C(CH_3)_2CH_2S(O)_2CH_3$	-CH_2OH	1.11	30	5343	164	1

Analog 83	$-CH_2C(CH_3)_2CH_2S(O)_2CH_3$	$-CH_2OCH_2CH_3$	0.12	0.37	1924	9513	4
Example 144	$-(CH_2)_2NHC(O)NHCH(CH_3)_2$	$-CH_2OH$	0.37	3.33	1488	74	1
Analog 84	$-(CH_2)_2NHC(O)NHCH(CH_3)_2$	$-CH_2OCH_2CH_3$	0.37	10	2045	7512	7

*TNF below experimental background of 40 pg/mL

Analogs 1-11, 17-33, 68, 72, and 77 are either specifically exemplified in or are readily prepared using the synthetic methods disclosed in U.S. Patent Nos. 6,331,539 and 6,677,349.

Analogs 12-16, 40-42, 46-50, 56, 57, 62, 63, 66, and 67 are either specifically exemplified in or are readily prepared using the synthetic methods disclosed in U.S. Patent Nos. 6,541,485 and 6,573,273.

Analogs 32-35 and 83 are either specifically exemplified in or are readily prepared using the synthetic methods disclosed in U.S. Patent No. 6,664,264.

Analogs 36-39 are either specifically exemplified in or are readily prepared using the synthetic methods disclosed in U.S. Patent No. 6,683,088.

Analogs 43-45, 58, 59, 70, and 73 are either specifically exemplified in or are readily prepared using the synthetic methods disclosed in U.S. Patent Nos. 6,069,149 and 6,677,349.

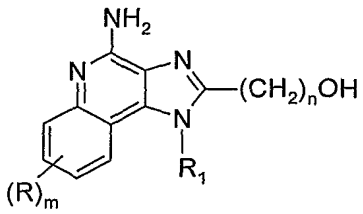
Analogs 52-55, 60, 61, 64, 65, 69, 71, 74, 75, 78, and 82 are either specifically exemplified in or are readily prepared using the synthetic methods disclosed in U.S. Patent Nos. 6,451,810 and 6,756,382.

Analogs 79-81 are either specifically exemplified in or are readily prepared using the synthetic methods disclosed in U.S. Patent No. 6,664,265.

The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. It should be understood that this invention is not intended to be unduly limited by the illustrative embodiments and examples set forth herein and that such examples and embodiments are presented by way of example only with the scope of the invention intended to be limited only by the claims set forth herein as follows.

WHAT IS CLAIMED IS:

1. A compound of the Formula I:



I

wherein:

m is 0 or 1;

n is 1 or 2;

R is selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkoxy, halogen, and C_{1-10} haloalkyl;

R_1 is selected from the group consisting of:

-X-Y-R_4,

-X-R_5, and

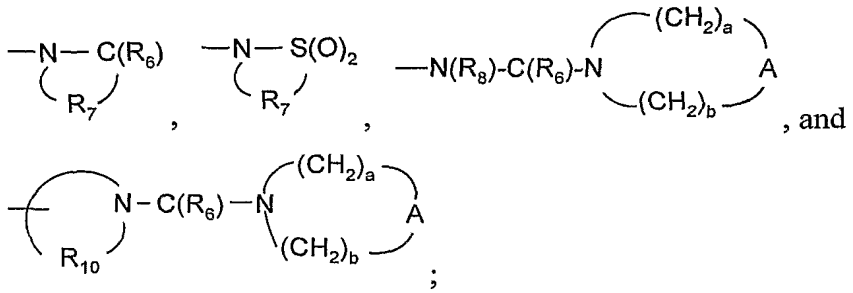
-X-Het;

X is straight chain or branched chain alkylene optionally interrupted by one -O- group;

Y is selected from the group consisting of -$S(O)_{0-2}$-and -$N(R_8)$-Q-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, and heteroarylalkylenyl, wherein the alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, and heteroarylalkylenyl, groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclyl, amino, alkylamino, dialkylamino, and in the case of alkyl and alkenyl, oxo;

R_5 is selected from the group consisting of:



Het is selected from the group consisting of tetrahydropyranyl and tetrahydrofuranyl;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

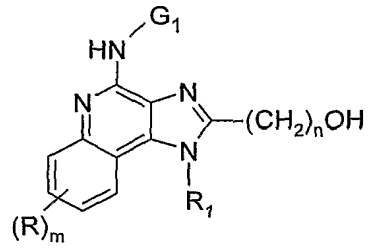
Q is selected from the group consisting of a bond, $-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-S-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

with the proviso that when Y is $-S(O)_{0-2}-$ then X can not contain an -O- group;

or a pharmaceutically acceptable salt thereof.

2. A compound of the Formula II:



II

wherein:

G_1 is selected from the group consisting of:

-C(O)-R',

α-aminoacyl,

α-aminoacyl-α-aminoacyl,

-C(O)-O-R',

-C(O)-N(R")R',

-C(=NY')-R',

-CH(OH)-C(O)-OY',

-CH(OC_{1-4} alkyl)Y_0,

-CH_2Y_1, and

-$CH(CH_3)Y_1$;

R' and R" are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, phenyl, benzyl, and 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, aryl-C_{1-4} alkylenyl, heteroaryl-C_{1-4} alkylenyl, halo-C_{1-4} alkylenyl, halo-C_{1-4} alkoxy, -O-C(O)-CH_3, -C(O)-O-CH_3, -C(O)-NH_2, -O-CH_2-C(O)-NH_2, -NH_2, and –$S(O)_2$-NH_2, with the proviso that R" can also be hydrogen;

α-aminoacyl is an α-aminoacyl group derived from an amino acid selected from the group consisting of racemic, D-, and L-amino acids;

Y' is selected from the group consisting of hydrogen, C_{1-6} alkyl, and benzyl;

Y_0 is selected from the group consisting of C_{1-6} alkyl, carboxy-C_{1-6} alkylenyl, amino-C_{1-4} alkylenyl, mono-*N*-C_{1-6} alkylamino-C_{1-4} alkylenyl, and di-*N,N*-C_{1-6} alkylamino-C_{1-4} alkylenyl;

Y_1 is selected from the group consisting of mono-*N*-C_{1-6} alkylamino, di-*N,N*-C_{1-6} alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C_{1-4} alkylpiperazin-1-yl;

m is 0 or 1;

n is 1 or 2;

R is selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkoxy, halogen, and C_{1-10} haloalkyl;

R_1 is selected from the group consisting of:

-X-Y-R_4,

-X-R_5, and

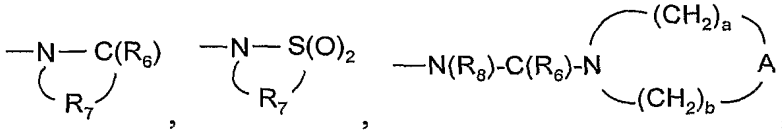
-X-Het;

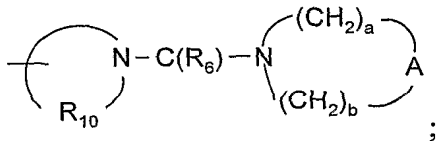
X is straight chain or branched chain alkylene optionally interrupted by one -O- group;

Y is selected from the group consisting of -$S(O)_{0-2}$-and -$N(R_8)$-Q-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, and heteroarylalkylenyl, wherein the alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, and heteroarylalkylenyl, groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclyl, amino, alkylamino, dialkylamino, and in the case of alkyl and alkenyl, oxo;

R_5 is selected from the group consisting of:





Het is selected from the group consisting of tetrahydropyranyl and tetrahydrofuranyl;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_{10} is C_{3-8} alkylene;

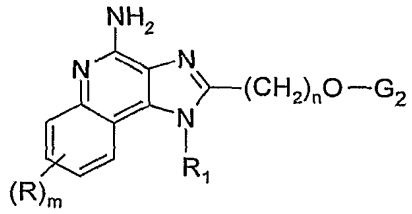
A is selected from the group consisting of -O-, -C(O)-, -CH_2-, -$S(O)_{0-2}$-, and -$N(Q\text{-}R_4)$-;

Q is selected from the group consisting of a bond, -$C(R_6)$-, -$S(O)_2$, -$C(R_6)$-$N(R_8)$-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, and -$C(R_6)$-S-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

with the proviso that when Y is -$S(O)_{0-2}$- then X can not contain an -O- group; or a pharmaceutically acceptable salt thereof.

3. A compound of the Formula III:



III

wherein:

G_2 is selected from the group consisting of:

$-X_2-C(O)-R'$,

α-aminoacyl,

α-aminoacyl-α-aminoacyl,

$-X_2-C(O)-O-R'$,

$-C(O)-N(R'')R'$, and

$-S(O)_2-R'$;

X_2 is selected from the group consisting of a bond; $-CH_2-O-$; $-CH(CH_3)-O-$; $-C(CH_3)_2-O-$; and, in the case of $-X_2-C(O)-O-R'$, $-CH_2-NH-$;

R' and R'' are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, phenyl, benzyl, and 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, aryl-C_{1-4} alkylenyl, heteroaryl-C_{1-4} alkylenyl, halo-C_{1-4} alkylenyl, halo-C_{1-4} alkoxy, $-O-C(O)-CH_3$, $-C(O)-O-CH_3$, $-C(O)-NH_2$, $-O-CH_2-C(O)-NH_2$, $-NH_2$, and $-S(O)_2-NH_2$, with the proviso that R'' can also be hydrogen;

α-aminoacyl is an α-aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids;

m is 0 or 1;

n is 1 or 2;

R is selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkoxy, halogen, and C_{1-10} haloalkyl;

R_1 is selected from the group consisting of:

$-X-Y-R_4$,

$-X-R_5$, and

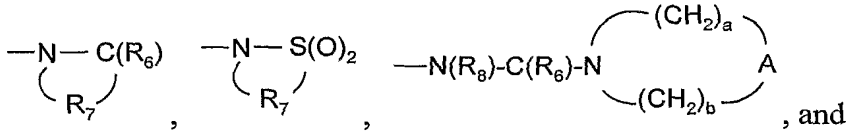
-X-Het;

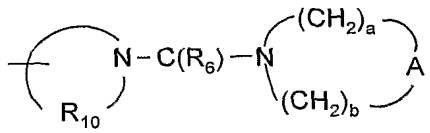
X is straight chain or branched chain alkylene optionally interrupted by one -O- group;

Y is selected from the group consisting of -$S(O)_{0-2}$-and -$N(R_8)$-Q-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, and heteroarylalkylenyl, wherein the alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, and heteroarylalkylenyl, groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclyl, amino, alkylamino, dialkylamino, and in the case of alkyl and alkenyl, oxo;

R_5 is selected from the group consisting of:


, and


;

Het is selected from the group consisting of tetrahydropyranyl and tetrahydrofuranyl;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, -CH_2-, -$S(O)_{0-2}$-, and -$N(Q-R_4)$-;

Q is selected from the group consisting of a bond, -$C(R_6)$-, -$S(O)_2$, -$C(R_6)$-$N(R_8)$-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, and -$C(R_6)$-S-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

with the proviso that when Y is -$S(O)_{0-2}$- then X can not contain an -O- group;

or a pharmaceutically acceptable salt thereof.

4. The compound or salt of any one of claims 1, 2, and 3, wherein n is 1.

5. The compound or salt of any one of claims 1, 2, and 3 wherein n is 2.

6. The compound or salt of any one of claims 1 through 5 wherein m is 0.

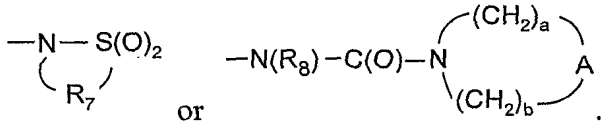
7. The compound or salt of any one claims 1 through 6 wherein R_1 is -X-Y-R_4 wherein X is straight chain or branched chain C_{1-6} alkylene which may be interrupted by one -O- group; Y is selected from the group consisting of -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, -N(R_8)-C(O)-N(R_8)-, and -S(O)$_2$- wherein R_8 is selected from hydrogen and methyl; and R_4 is selected from the group consisting of C_{1-6} alkyl, isoquinolinyl, *N*-methylimidazolyl, pyridinyl, quinolinyl, phenyl, and phenyl substituted by a substituent selected from the group consisting of chloro, cyano, fluoro, hydroxy, and methyl.

8. The compound or salt of any one of claims 1 through 7 wherein R_1 is selected from the group consisting of 2-[(cyclopropylcarbonyl)amino]ethyl, 4-[(cyclopropylcarbonyl)amino]butyl, 2-[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-{[(1-methylethyl)carbonyl]amino}ethyl, 4-{[(1-methylethyl)carbonyl]amino}butyl, 2-methyl-2-{[(1-methylethyl)carbonyl]amino}propyl, 2-[(methylsulfonyl)amino]ethyl, 4-[(methylsulfonyl)amino]butyl, 2-methyl-2-[(methylsulfonyl)amino]propyl, 2-methyl-2-({[(1-methylethyl)amino]carbonyl}amino)propyl, and 2,2-dimethyl-3-(methylsulfonyl)propyl.

9. The compound or salt of any one claims 1 through 6 wherein R_1 is -X-Y-R_4 wherein X is straight chain or branched chain C_{1-8} alkylene which may be interrupted by one -O- group; Y is selected from the group consisting of -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, -N(R_8)-C(O)-N(R_{8a})-, and -S(O)$_2$- wherein R_8 is hydrogen, methyl, benzyl, or pyridin-3-ylmethyl; R_{8a} is hydrogen, methyl, or ethyl, and R_4 is selected from the group consisting of C_{1-7} alkyl, haloC_{1-4} alkyl, hydroxyC_{1-4} alkyl, phenyl, benzyl, 1-phenylethyl, 2-phenylethyl, 2-phenylethenyl, phenylcyclopropyl, pyridinyl, thienyl, *N*-methylimidazolyl, 3,5-dimethylisoxazolyl, wherein benzyl is unsubstituted or substituted by a methyl group, and

phenyl is unsubstituted or substituted by one or two substituents independently selected from the group consisting of methyl, fluoro, chloro, cyano, hydroxy, and dimethylamino.

10. The compound or salt of any one of claims 1 through 6 wherein R_1 is -X-R_5 wherein X is C_{1-6} alkylene, and R_5 is



or

.

11. The compound or salt of any one of claims 1 through 6 or 10 wherein R_1 is selected from the group consisting of 4-(1,1-dioxidoisothiazolidin-2-yl)butyl, 4-[(4-morpholinecarbonyl)amino]butyl, and 2-[(4-morpholinecarbonyl)amino]ethyl.

12. The compound or salt of any one of claims 1 through 6 wherein R_1 is -C_{1-4} alkylenyl-Het.

13. The compound or salt of any one of claims 1 through 6 or 12 wherein R_1 is tetrahydro-2*H*-pyran-4-ylmethyl.

14. A compound selected from the group consisting of *N*-[4-(4-amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]methanesulfonamide and *N*-{4-[4-amino-2-(2-hydroxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl]}methanesulfonamide, or a pharmaceutically acceptable salt thereof.

15. *N*-{2-[4-Amino-2-(hydroxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1,1-dimethylethyl}methanesulfonamide or a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of any one of claims 1 through 15 and a pharmaceutically acceptable carrier.

17. A method of preferentially inducing the biosynthesis of IFN-α in an animal comprising administering an effective amount of a compound or salt of any one of claims 1 through 15 or a pharmaceutical composition of claim 16 to the animal.

18. A method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of claims 1 through 15 or the pharmaceutical composition of claim 16 to the animal.

19. A method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of claims 1 through 15 or the pharmaceutical composition of claim 16 to the animal.

20. The method of any one of claims 17, 18, or 19 wherein the compound or salt or pharmaceutical composition is administered systemically.

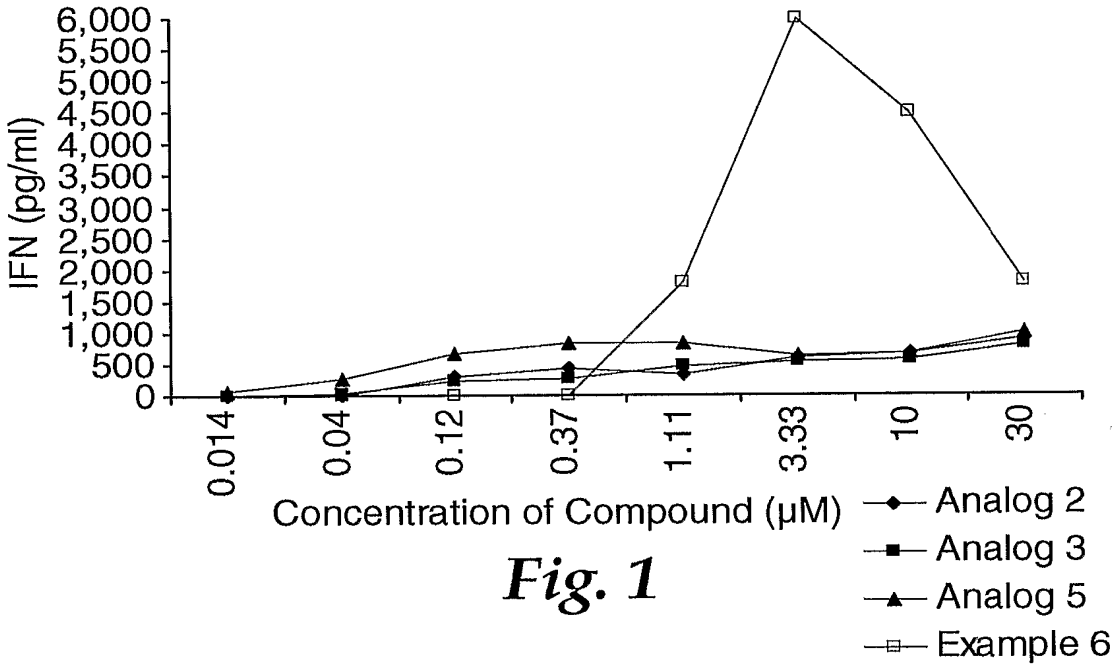

IFN (pg/ml)
6,000
5,500
5,000
4,500
4,000
3,500
3,000
2,500
2,000
1,500
1,000
500
0
0.014
0.04
0.12
0.37
1.11
3.33
10
30
Concentration of Compound (μM)
Analog 2
Analog 3
Analog 5
Example 6

Fig. 1

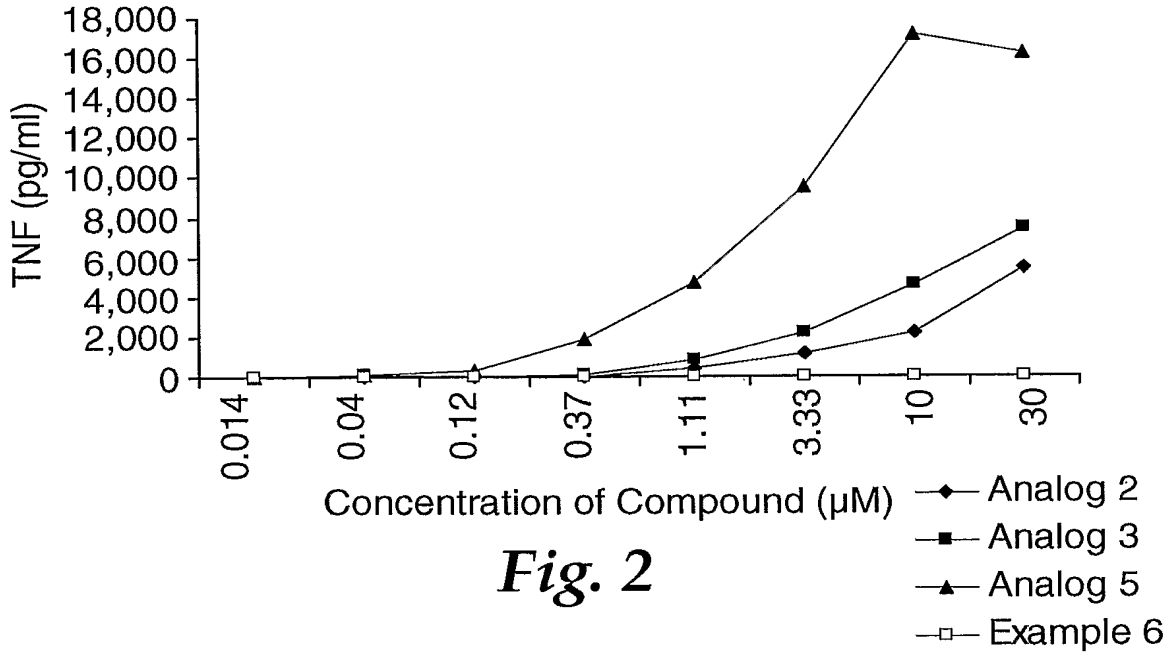

TNF (pg/ml)
18,000
16,000
14,000
12,000
10,000
8,000
6,000
4,000
2,000
0
0.014
0.04
0.12
0.37
1.11
3.33
10
30
Concentration of Compound (μM)
Analog 2
Analog 3
Analog 5
Example 6

Fig. 2

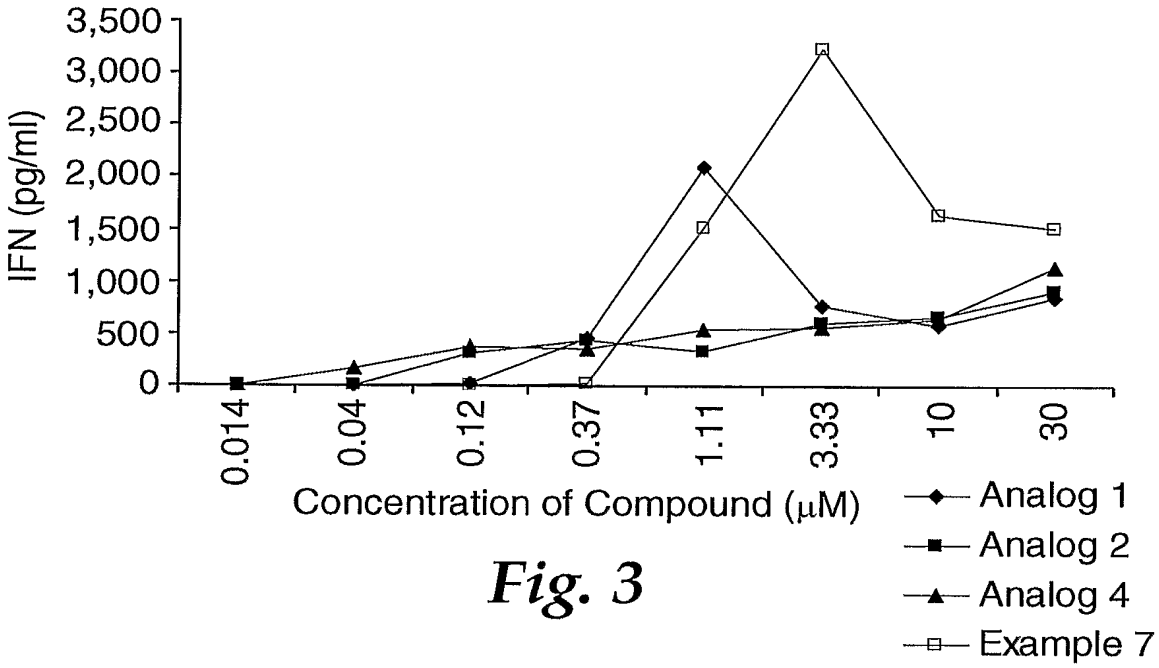

3,500
3,000
2,500
2,000
1,500
1,000
500
0
IFN (pg/ml)
0.014
0.04
0.12
0.37
1.11
3.33
10
30
Concentration of Compound (μM)
Analog 1
Analog 2
Analog 4
Example 7

Fig. 3

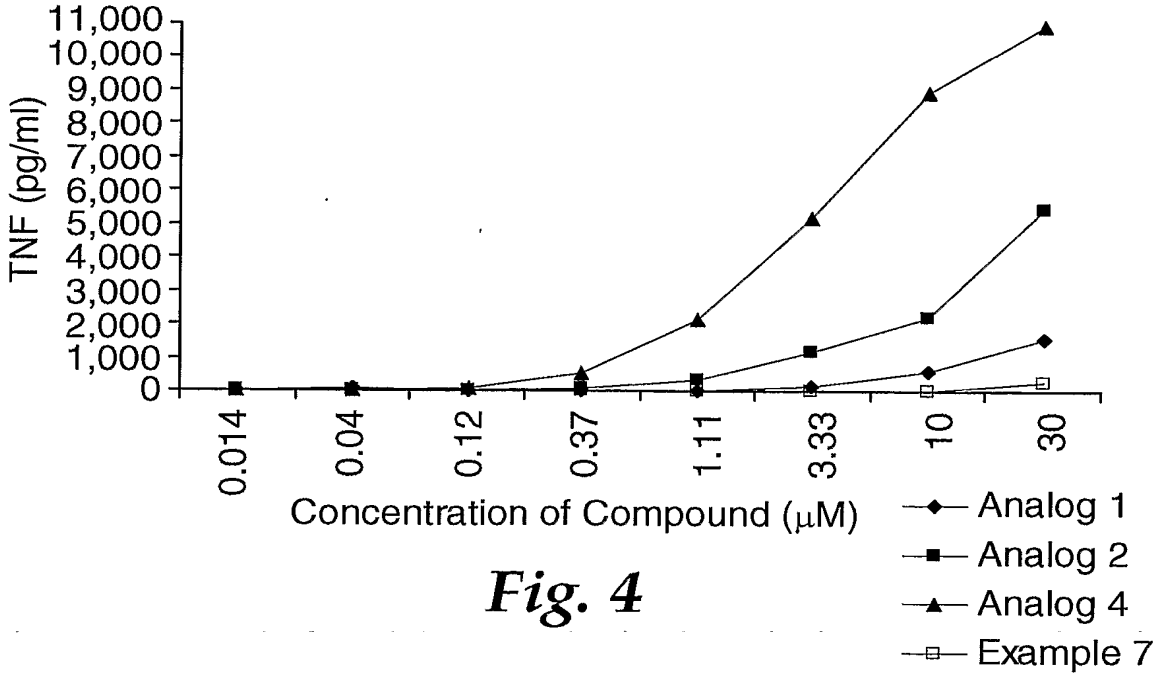

11,000
10,000
9,000
8,000
7,000
6,000
5,000
4,000
3,000
2,000
1,000
0
TNF (pg/ml)
0.014
0.04
0.12
0.37
1.11
3.33
10
30
Concentration of Compound (μM)
Analog 1
Analog 2
Analog 4
Example 7

Fig. 4